COMPARING THE DEGREE OF AGREEMENT OF INTRAOCULAR PRESSURES IN PATIENTS WITH KERATOCONUS USING GOLDMANN APPLANATION TONOMETER, DYNAMIC CONTOUR TONOMETRY & TONOPEN

DISSERTATION SUBMITTED AS PART OF FULFILMENT FOR THE MS BRANCH III (OPHTHALMOLOGY) DEGREE EXAMINATION OF THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY, TO BE HELD IN APRIL 2015

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled “To compare the degree of agreement of intraocular pressures in patients with Keratoconus using Goldmann Applanation Tonometry, Dynamic Contour Tonometry & Tonopen ” done towards fulfilment of the requirements of the Tamil Nadu Dr. MGR Medical University, Chennai, for the MS Branch III (Ophthalmology) examination to be conducted in April 2015, is a bona fide work of Dr.Shishir Verghese, postgraduate student in the Department of Ophthalmology, Christian Medical College, Vellore.

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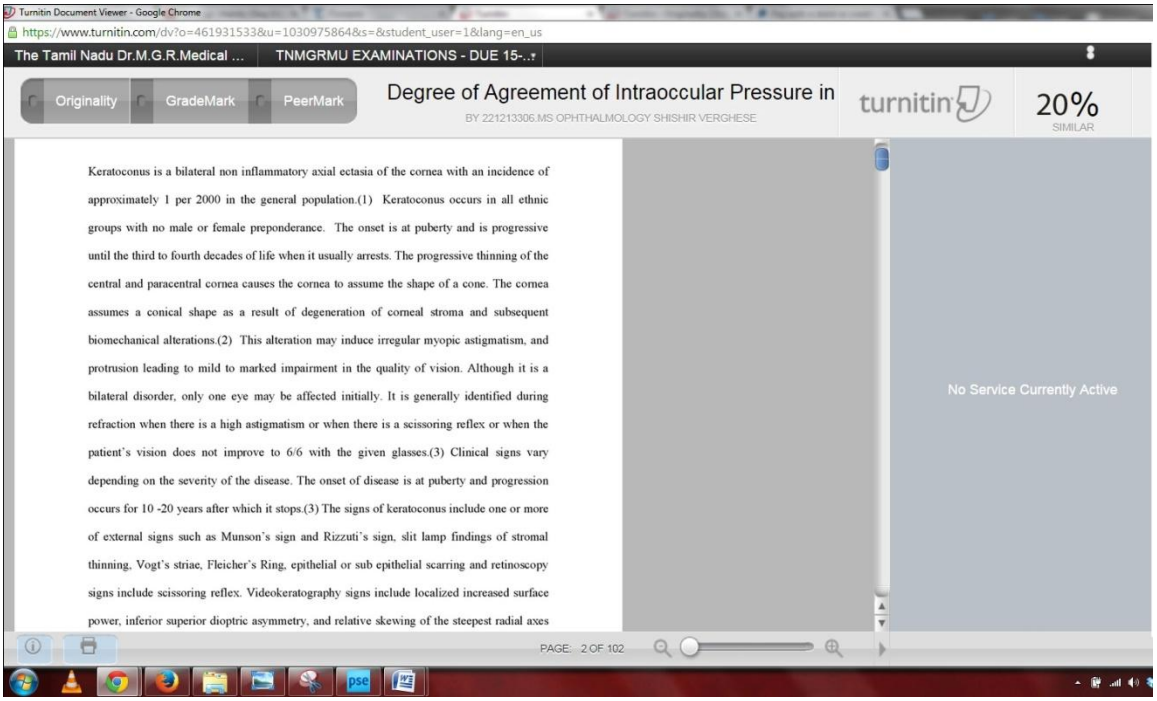

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INTRODUCTION

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CONTENTS

Degree of Agreement of Intraocular pressures in patients with keratoconus using Goldman Applanation Tonometer, Dynamic Contour Tonometer and Tonopen

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Abstract

Aim: The aim of this study was to measure and compare the intraocular pressure (IOP) in patients with keratoconus using Goldman Applanation Tonometer (GAT), Dynamic Contour Tonometer (DCT) and Tonopen and evaluate the possible influence of central corneal thickness (CCT) on the intraocular pressure measured with the three tonometers.

Methods: This was a prospective case control study of 41 keratoconus patients and 100 normal patients where the intraocular pressure was measured with the GAT, DCT and Tonopen. CCT was measured with an ultrasound pachymeter.

Results: The mean IOP as obtained with GAT, DCT and Tonopen was 12.06 ± 2.12, 14.83 ± 2.49, 12.34 ± 1.88 in keratoconus and 13.94 ± 1.96, 14.22 ± 2.04 and 13.36 ± 1.70 in normals respectively. The mean difference in IOP between tonometers was different for cases and controls and this was shown to be statistically significant ($p<0.001$) DCT tended to overestimate the IOP in both groups. In both keratoconus and controls a fair to good agreement was shown between GAT and DCT, an excellent agreement between Tonopen and GAT and a fair agreement between DCT and Tonopen ($p<0.001$). There was no correlation between the CCT with the IOP with all three tonometers in both groups, however a clinical

significant correlation was seen with GAT more in cases than controls. IOP values were found to be reproducible with all three tonometers.

Conclusion: All three methods of measuring IOP with GAT, Tonopen and DCT showed fair to good correlation, with an excellent agreement shown between GAT and Tonopen. Intraocular pressure measured with DCT and CCT corrected IOP measured with GAT are recommended as suitable methods for IOP measurement for keratoconus patients. It is also important to choose an instrument which is best suited for a particular patient and should be consistently used for the long term follow up. There was no influence of CCT on IOP measurements with the three tonometers in keratoconus. All three methods of IOP were found to be reproducible.

Keywords : Keratoconus, Intraocular pressure, Goldmann Applanation Tonometer, Dynamic Contour Tonometer, Tonopen, Central Corneal Thickness

INTRODUCTION

Keratoconus

Keratoconus is a bilateral non inflammatory axial ectasia of the cornea with an incidence of approximately 1 per 2000 in the general population.(1) Keratoconus occurs in all ethnic groups with no male or female preponderance. The onset is at puberty and is progressive until the third to fourth decades of life when it usually arrests. The progressive thinning of the central and paracentral cornea causes the cornea to assume the shape of a cone. The cornea assumes a conical shape as a result of degeneration of corneal stroma and subsequent biomechanical alterations.(2) This alteration may induce irregular myopic astigmatism, and protrusion leading to mild to marked impairment in the quality of vision. Although it is a bilateral disorder, only one eye may be affected initially. It is generally identified during refraction when there is a high astigmatism or when there is a scissoring reflex or when the patient's vision does not improve to 6/6 with the given glasses.(3) Clinical signs vary depending on the severity of the disease. The onset of disease is at puberty and progression occurs for 10 -20 years after which it stops.(3) The signs of keratoconus include one or more of external signs such as Munson's sign and Rizzuti's sign, slit lamp findings of stromal thinning, Vogt's striae, Fleicher's Ring, epithelial or sub epithelial scarring and retinoscopy signs include scissoring reflex. Videokeratography signs include localized increased surface power, inferior superior dioptric asymmetry, and relative skewing of the steepest radial axes above and below the horizontal meridian. Other accompanying signs might include epithelial nebulae, anterior stromal scars, enlarged corneal nerves, increased intensity of the corneal endothelial reflex and sub epithelial fibrillary lines.

Symptoms are highly variable and depend on the stage of progression of the disorder with the patient having no symptoms early on in the disease. Hence the early forms of the disease may go undetected unless anterior corneal topography is studied.

In the past 30 years computer technology and biotechnology has had a major influence in improving our understanding as well as in the diagnosis and management of keratoconus.

Many devices are available for measuring the anterior corneal topography, with computer assisted videokeratography which generate colour coded maps. Topographic indices are currently the most sensitive and sophisticated devices for confirming the diagnosis of keratoconus.(1)

Management options include treatment with contact lenses, collagen cross linking, intrastromal ring segments, thermokeratoplasty and in severe cases lamellar or penetrating keratoplasty.

Recording and monitoring of Intra Ocular Pressure (IOP) is essential in patients with keratoconus. Glaucoma or ocular hypertension may co-exist in patients with keratoconus and following penetrating keratoplasty or refractive surgery for keratoconus. After penetrating keratoplasty, up to 30% of patients may have raised IOP or glaucoma, risking both optic nerve damage and graft failure. It is therefore important that reliable measurement of IOP is made in these patients to assist in the diagnosis and monitoring of treatment.

Goldmann Applanation Tonometry (GAT) is the gold standard for measurement of IOP. The effect of Central Corneal Thickness (CCT) on the accuracy of IOP measurement was suggested in 1957. GAT IOP measurement varies with the CCT. In ketatoconus thinner cornea with structural changes causing changes in corneal rigidity as well as increased corneal steepness and curvature makes GAT not the most suitable method to check IOP. The corneal curvature may make measurements difficult

especially in cases of advanced keratoconus due to larger applanating area and the IOP measurement may not be consistent due to the variability in corneal thickness and alteration in ocular surface. Hence the search for better, reproducible methods of measuring IOP which is least influenced by factors like central corneal thickness, corneal curvature, corneal irregularity, corneal rigidity and corneal hysteresis. To overcome these problems involved in estimating the IOP in eyes with keratoconus, studies have looked into the measurement and variation of IOP as measured by other methods of tonometry like Tonopen, Dynamic Contour Tonometry (DCT) and the Ocular Response Analyzer (ORA) which may be more suited for eyes with keratoconus.

The **Tonopen** is a hand held battery operated instrument and has a smaller applanating surface as compared to GAT. Most studies agree that there is good correlation with GAT IOP especially within the normal range of IOP.(4–8) Studies have also shown that the Tonopen is relatively independent of the CCT especially in patients with Keratoconus and post penetrating Keratoplasty.(9) In eyes with increased CCT (>584 μm), the tonoPen tended to produce, consistently, higher IOP readings than GAT. (10)

DCT is a relatively new digital tonometer that uses the principle of contour matching instead of applanation. Studies have found that IOP as measured by DCT is relatively independent of CCT, corneal curvature or axial length.(11–13) It has also been found to be accurate in eyes with keratoconus(14–16) corneal oedema (17) and post penetrating keratoplasty.(16)

There are various studies comparing the IOP as measured with different tonometers in keratoconic eyes. However there are no studies in Indian eyes comparing the three tonometers namely GAT, DCT and Tonopen and the factors influencing the IOP in keratoconic eyes. Since IOP measurement is an important part of management and follow up of patients with keratoconus we conducted this study to decide which among the three tonometers would be ideal to measure IOP in these patients.

AIMS & OBJECTIVES

Aims

- To measure and compare the IOP in patients with keratoconus and normals using three methods: GAT, Tonopen and DCT.
- To measure the (CCT) in these patients and look for the possible influence of CCT on the IOP measured by the three methods mentioned above.

Objectives

- To measure the IOP in patients with keratoconus (cases) and in normals (controls) using three methods : GAT, DCT and Tonopen and correlate the degree of agreement between them
- To measure the CCT using ultrasound pachymetry in cases and controls and evaluate the possible influence of CCT on IOP measured by the three instruments.
- To measure the intraocular pressure in patients with keratoconus (cases) and in normals (controls) using the same three methods as mentioned above after one hour to look for the reproducibility of the instruments in measuring the intraocular pressure.

REVIEW OF LITERATURE

Review of literature

Keratoconus

Keratoconus is an ectatic non inflammatory corneal disorder, usually bilateral, characterised by a progressive corneal protrusion and decreased vision. There is central corneal thinning, the apex of the cone usually centred just below the visual axis, associated with irregular astigmatism and myopia due to the progressive corneal protrusion.

It was first described in the year 1850 by a British physician John Nottingham. (18) Though an uncommon disorder the estimated incidence reported is approximately 1 per 2000 in the general population with higher incidence in refractive surgery candidates.(1,19,20) A prevalence study from Maharashtra, in central India, reported a prevalence rate of 2.3%.(21)

Classically the disease starts in the adolescent age group and progresses through the third and fourth decade of life.(1,3,21,22) It is a condition associated with a progressive degeneration of corneal stroma due to changes in the biochemical properties of the cornea. (1,23–29)

Corneal structure in keratoconus

Every layer of the cornea is involved in the pathological process of keratoconus.(3) The epithelium may show degeneration of its basal cells, and accumulation of ferritin particles within and between epithelial cells most prominently in the basal layer of the epithelium. Features noted in the stroma are compaction and loss of arrangement of fibrils in the anterior stroma. Descemet's membrane is rarely affected except for breaks seen in acute hydrops. The endothelium is usually normal. The presence of two types of cone morphology: "nipple"-type cones, located centrally, and "oval"-(sagging) type cones, located inferiorly or

inferotemporally have been revealed. These types of cones often can be distinguished on slit-lamp examination or evaluation of the anterior corneal topography in keratoconus patients.(1) Ectatic conditions of the cornea such as keratoconus are progressive. There is distortion of corneal curvature and is thought to be associated with weaker corneas. There is evidence that both the anterior and posterior curvatures are affected in keratoconus and in suspects. The stromal thinning and posterior stress line, suggest that posterior surface geometry may be altered independent of the anterior corneal surface even in the early stage of disease.(2)

Recent models of keratoconus pathogenesis have postulated that the biochemical alteration may be the consequence of the distortion of the lamellar matrix in the stroma which does not follow the orthogonal pattern, thus there are regions of highly aligned collagen intermixed with regions in which the collagen alignment is poor.(2)

Keratocyte apoptosis and abnormal regulation of collagenase, protease and tissue inhibitors of matrix metalloproteinases-1 and -3 may play a role in the development of stromal ultra structural defects. Even though there has been progress in the understanding of the biomechanical properties of the condition, when it comes to diagnosis and treatment there is limitation in measuring the biomechanical properties due to lack of availability of reliable equipment as of yet.(30–33)

Corneal thickness in keratoconus

Classification and detection techniques for keratoconus

The diagnosis involves a careful clinical examination followed by biomicroscopy, keratometry, keratoscopy, pachymetry and computer assisted topography. Clinical diagnosis of moderate to advanced is not difficult because of the presence of the classic retinoscopy and

biomicroscopy signs. However, identification of early cases (forme fruste) with no specific corneal findings is challenging.

Diagnosing the early disease is important for screening patients for refractive surgery. Keratoconus suspects are cases which do not show biomicroscopic signs but only subtle topographic changes.(2) Rapid evolution of corneal imaging technology has led to the progress in geometric characterisation of keratoconus.

A newer nomenclature has been proposed which combines information from genetics, biochemistry, tomography and biomechanics; which are obtained from diagnostic tests. Five states have been recognized in the new nomenclature which are progressive symptomatic keratoconus, non progressive symptomatic keratoconus, progressive asymptomatic, non progressive asymptomatic and keratoconus suspect. (36)

Various keratoconus diagnosis, staging, and progression criteria are in clinical use. These include data from clinical evaluation, topography and topometry derived indicators.

Clinical data include distance uncorrected visual acuity (UCVA), and best corrected visual acuity (BCVA) and manifest refractive spherical equivalent (MRSE). Quantitative and qualitative topographic and topometric measurements include keratometry (K), anterior and posterior corneal elevation, curvature asymmetry, and corneal pachymetry. These parameters can be incorporated in various decision-tree schemes and/or staging keratoconus classification systems, such as the Rabinowitz, Klyce, and Amsler- Krumeich criteria.(37–39) Clinical experience with keratoconus screening and management, however, suggests that corneal pachymetry and visual acuity measurements may not always be reliable indicators of ectasia or keratoconus progression.

The assessment of keratoconus severity and visual function has yielded poor results in keratoconic eyes when compared with several anterior-surface–derived topographic parameters, including K, pachymetry, and surface-asymmetry indices.(19,38,40)

Other published reports also indicate the limitations in specificity and sensitivity of traditionally employed keratoconus criteria.4,8,9

Thus, the refinement and augmentation of early diagnostic criteria for keratoconus is of clinical significance because it may enable more timely intervention(41)

The Gold standard grading scheme proposed by Mc Mohan et al was in use which classified keratoconus into keratoconus suspect, mild, moderate and severe keratoconus.(42)

Rabinowitz described a classification scheme of keratoconus suspect, early keratoconus and keratoconus. Their classification was based on the analysis of the topographic data such as KISA % index where K is the central K reading, I-S is the inferior superior steepening, A is the AST index (Sim K1 –SimK2)(43)

Mahmoud et al proposed the cone location and magnitude index and Maeda et al proposed the keratoconus prediction index and keratoconus index. Smolek and Klyce developed neural classification indices and Chastang et al developed a binary decision tree on the basis of topographic indices.(38,44,45)

Advance imaging technologies like the optical coherence tomographers, systems combining the scanning slit and Placido disk technologies, and systems based on the Scheimpflug photography techniques are commercially available. These systems allow the pachymetry distribution as well as the evaluation of the volume of the cornea.

These technologies are based on an expert system classifier which is able to determine whether the map shows a keratoconus like pattern using the binary classification tree and, if so, a value between 1% and 100% (the KCI) in proportion to the linear discriminate function

to quantify the severity of keratoconus or no keratoconus like pattern is reported. Thus keratoconus can be differentiated from a wide range of pathologies. The false positive rate of 1 out of 43 and a false negative rate of 2 in 130 was reported .(1, 3)

A Scheimpflug camera combined with a placido disc topographer (Sirius, CSO, Italy) incorporates a software which helps to detect keratoconus, sub clinical, suspects and normals using the support vector machine (SVM) technique.(46)

The Klyce Madea Classification system:

This system uses indices like SimKl, SimK2, and Surface Asymmetry Index (SAI)—and five new indices—the Differential Sector Index (DSI), the Opposite Sector lndex (OSI), the Center/Surround Index (CSI), the Irregular Astigmatism Index (I A I), and the Analyzed Area (AA)..

This system combines a classification tree with a linear discriminated function derived from discriminate analysis yielding a single composite discriminate value for each map known as Keratoconus Prediction Index (KPI). The KPI value is the index that is proportional to the discriminate value cut off value obtained from the discriminant function.. Maps which show a KPI value greater than the optimum cut-off are classified as keratoconus, whereas maps with a KPI value of less than the optimum cut-off value are classified as non keratoconus.

Various Alogrithms used for detecting and classifying keratoconus

Alogrithms	Indices Used	Comments
Rabinowitz	Central K, I-S value, Sim K & SRAX index	Could only differentiate Keratoconus from normals
Klyce Madea	SimKl, SimK2, and SAI five new indices : DSI, OSI,CSI, I A I & the AA	Differentiated keratoconus from normals and other pathologies as well
Smolek Klyce (Neural Network approach	SimKl, SimK2, and SAI five new indices : DSI, OSI,CSI, I A I & the AA	One network detects and classifies clinical keratoconus & keratoconus suspects from confounding topographic patterns. 2nd network quantifies the severity of cone that matches the topographic pattern of clinical keratoconus or keratoconus suspects
KISA%	KISA% = (K) x (I–S) x (AST) x (SRAX) X 100	Identifies normal eyes, keratoconus suspects & those with disease. It is used to monitor changes in normal eyes of unilateral keratoconus patients and in genetic screening, where it was used to distinguish keratoconus from normal individuals

Intraocular pressure (IOP) in keratoconus

Structural changes of the cornea in keratoconus lead to difficulties in the accurate measurement of intraocular pressure by applanation tonometry and therefore IOP reading is generally lower than expected.(27) Generally keratoconus is a condition which is associated with a low intraocular pressure and is not thought to be associated with glaucoma.(28,35)

However in hospitals where keratoconus patients are referred for evaluation a greater number have been diagnosed as glaucoma suspects and many of them have been found to develop glaucomatous optic neuropathy despite a normal IOP recording.

Accurate intra ocular pressure (IOP) measurements are important in keratoconus because glaucoma and keratoconus can co- exist.

Corneal parameters affecting IOP measurements with various tonometers

The corneal parameters are the main source of error in IOP measurement for all the devices but data is limited.(15,47,48) The morphological changes in keratoconus include alterations in the rigidity and elasticity of cornea and thinning of the central cornea in later stages of the disease however, the peripheral corneal thickness is probably unaffected. (1) A larger within the study co-efficient of variation (COV) was reported for keratoconus patients as compared to normals (12.3%,-range-5.7% to 27.4) from the perspective of meta analysis generated normative values for adult CCT. Pachymetry has been found to be useful in cases of keratoconus and other corneal degenerations survey opthal 2000.

An average CCT of 0.434 mm has been calculated from these studies which are clearly much lower than the values from normal corneas. These changes associated with keratoconus may potentially lead to difficulties in the accurate measurement of intraocular pressure by

applanation tonometry, the reading generally being lower than as expected.(49) Patients with severe keratoconus may present with acute hydrops which is characterized by presence of stromal oedema and hence in such condition, IOP measured was falsely low even though the corneal thickness was high.(17)

The Goldmann applanation tonometer is the gold standard for IOP measurements. However under and over estimations occur with this device when the corneal thickness is outside normal limits.(50,51)

This is because the Goldman applanation tonometer and other devices based on the principle of applanation for IOP measurement are affected by variations in the corneal thickness.(28,48,52,53)

Like the Goldmann tonometry, many studies have shown that corneal abnormalities influence the IOP measured by non contact tonometers. The dynamic contour tonometer (DCT) is expected to be unaffected by corneal properties.(15,54)

Firat et al[rr] conducted a study to determine the agreement between IOP readings obtained by GAT, non contact tonometer (NCT) and the DCT to determine the influence of corneal parameters like corneal thickness (CCT), thinnest corneal thickness (TCT), steepest Keratometry, corneal curvature(CC), corneal volume(CV) and posterior corneal curvature (PCC) on the IOP readings in keratoconus and normal eyes. They found that the IOP measurements were significantly different between the various tonometers in the keratoconus group as compared to the normals. In the keratoconus group the corneal parameters ie the thinnest corneal thickness, steepest keratometry, the corneal curvature, the CCT and posterior corneal curvature had a significant influence on the GAT and noncontact tonometer but not on the DCT. In the control group the thinnest corneal thickness and CCT influenced the GAT and noncontact tonometer but not the DCT.

Firat et al found that dynamic contour tonometer seemed to be unaffected by corneal parameters but the IOP readings measured with DCT as compared to other tonometers were significantly different in keratoconus patients from those in the normal eyes. The differences in the biochemical parameters of the keratoconic corneas as compared to the normal eyes could be responsible for this difference. Bayer et al(55) showed that the dynamic contour tonometer was significantly affected by corneal hysteresis and the corneal resistance factor in keratoconic eyes. This could be attributed to the design of the dynamic contour tonometer, which is not an applanation tonometer. The corneal geometrics and viscoelasticity of the keratoconic eyes could influence the conformable design of the DCT resulting in the difference in the accuracy of IOP measurement in keratoconic patients as compared to normals.

The corneal volume is significantly reduced due to corneal tissue loss during progression of keratoconus.(56,57) However none of the tonometers were affected by the corneal volume..

Modalities of tonometry and corneal thickness (10)

Intraocular pressure describes the tension exerted by the aqueous humor on the intraocular tissues due to a balance between the production and drainage. Precise IOP measurement is influenced by variables like the circadian rythem and the influence of corneal biochemical properties.

An easy to use and reliable and accurate tonometer is desirable for IOP measurements, the principle of applanation or indentation is the one on which most commercially available tonometers measure IOP. The force exerted on the external corneal surface is s the pressure at the level of the endothelium and therefore the pressure in the anterior chamber and vitreous

cavity. This is measured as the force applied (F) to the outer corneal (A). The pressure related to the corneal propertiesb(Pcp) and (tIOP) gives the true IOP measurements.

(Equation 1) F/A=Pcp+tIOP

This equation takes into consideration the fact that all individuals have identical corneal thickness and viscoelasticity. However corneal thickness and elastic properties of the cornea vary depending on the age, race, and corneal abnormalities or even between fellow eyes. Thus accurate IOP measurements depend on the corneal thickness, curvature and biomechanical properties.

Tonometers are of two types

1. Applanation – contact and non contact tonometers
2. Non applanation

Applanation tonometers

A. **Goldmann Applanation Tonometer**

B. This tonometer was developed in the 1950's and is based on the Imbert-Fick law. This law states that "The pressure in a sphere filled with fluid and surrounded by an infinitely thin and flexible membrane is measured by the counter pressure which just flattens the membrane to the plane". This being an hypothetical model Goldmann and Schmidt suggested that this would give precise results in the patients having an average central corneal thickness between 500 and 525 microns.

This tonometer is used worldwide and still remains the Gold standard for tonometry. It was found by the ocular hypertension study that eyes with thinner CCT are at increased risk of developing glaucoma. In eyes a CCT of less than 525µm, GAT tends to underestimate the

actual IOP, while in eyes with CCT of more than 555µm, it overestimates IOP.(58) There is no clear evidence to suggest that in case of irregular corneas and in patients post penetrating keratoplasty and refractive surgery there could be inaccuracies in IOP measurements. Similarly in keratoconus, high astigmatism and stromal scarring, GAT may show inaccurate readings due to inaccracy of CCT measurements. Brooks et al(59) stated that GAT measurements were significantly lower at the apex of the cone as compared to measurements taken at the flatter or thicker areas of the cornea. In keratoconus, the GAT measurements were approximately 5.3 ± 2.2 mm of Hg lower than that recorded by non applanation tonometry, which seemed to provide measurements closer the actual intraocular pressures.(14)

Similar findings have been reported by other authors in patients following penetrating keratoplasty, LASIK, LASEK and PRK. One should be aware in clinical settings that the IOP could be over or underestimated in situations with variations in CCT. Since GAT is the Gold standard for IOP estimation, all other tonometers are compared to readings of the GAT.

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C. Tono-Pen XL (Mentor O&O Inc; Norwell, MA, USA)

This is a light weight contact electronic applanation tonometer, which is portable and easy to calibrate and operate. Its digital monitor minimises user bias and due to its small contact area (2.36mm^2 compared to 7.35 mm^2 in GAT), it is recommended for IOP measurements in irregular corneas. It is also useful when patient is not cooperative, allowing measurements in both supine and sitting positions. A minimum of four measurements is necessary to get an average value. It also provides a coefficient of variation which ideally should be less than five for a measurement to be considered accurate.

However studies have shown that Tonopen does over or underestimate IOP without a consistent pattern. Salvetat et al(60) found that Tonopen underestimated GAT by 0.5 ± 4.5 mmHg. In eyes with CCT>584 microns the Tonopen tends to consistently give readings, higher than GAT. With regard to irregular corneas Mollan et al(9) evaluated IOP with four different tonometers in eyes with keratoconus and found that Tonopen overestimated GAT by 3.6 ± 10.1mmHg. He also found in this group of patients that as compared to GAT readings the Tonopen overestimated IOP values for lower IOPs (by GAT) and underestimated the higher IOPs compared to the GAT measurements. It seemed to be less dependent on CCT in keratoconus that GAT. Though it may prove useful in irregular corneas due to its smaller contact area the results should be interpreted with caution especially in eyes with increased CCT.

D. Perkins Handheld Tonometer (Medtronic Solan, Jacksonville, FL, USA)

The Perkins applanation tonometer is a portable handheld device, considered to be the gold standard for portable tonometry. Few studies have shown a close agreement between the Perkins tonometer and GAT.(61,62) with a mean difference of 1.0 mmHg between the two tonometers.(61)

It is useful for the determination of the daily curve of IOP in the supine position. As breath-holding (required for GAT measurements, taken in sitting position) and thus thorax compression may cause transitory elevations of IOP, the Perkins tonometer may provide more reliable measurements in cases where a transitory high IOP is recorded in sitting position if patient is overweight and has breath holding.(63)

E. Corneal Hysterisis & the Ocular Response Analyser (Reichert Ophthalmic Instruments, Depew, New York, USA

Corneal Hysteresis (CH) is an indication of viscous dampening of the cornea, reflecting the capacity of the corneal tissue to absorb and dissipate energy. It is a biomechanical property(64) of the corneal tissue to recover its original shape after an external force is applied. CH is weakly correlated with CCT, is almost constant throughout the day(65) and seems un-associated with refractive error or axial length.(27,66)

Keratoconus corneas are associated with low corneal hysteresis.(9) The Ocular response analyser is an instrument capable of measuring the corneal hysteresis. It is a fully automated stand-alone non-contact tonometer with an electro-optical system that scans the central cornea. It uses a bi directional applanation process in which an air pulse deforms the cornea inwards past the applanation point. After the applanation point is detected the air is turned off and the cornea is allowed to return to normal. Two independent pressure values are derived from these applanation points. The difference between the two measurements (inward and outward applanation) is termed corneal hysteresis.

Based on this initial evaluation, the device provides 4 different parameters: Goldmann-correlated IOP, corneal-compensated IOP (IOPcc), corneal resistance factor (CRF) and corneal hysteresis (CH)(67). IOPcc measurements could provide an estimate of IOP that is less influenced by corneal properties than that provided by GAT.(27,64–69) Patients with lower CCT and CH values tend to have higher IOPcc values, compared to GAT results. Conversely, patients with higher CCT and CH values tend to get lower IOPcc values.(69,70) Furthermore, it was demonstrated that IOPcc was not correlated with CCT or corneal curvature, but it was positively associated with age.(71)

Even though the overall difference between GAT IOP and IOPcc was not significant, it tended to be bigger for increasing CCT values. ORA has been used in keratoconus to study the IOP, CRF and CH.(69)

F. Non-contact Tonometer or Air-puff Tonometer (Reichert Ophthalmic Instruments, Depew, New York, USA)

This is a non contact applanation tonometer initially created in the 1950's by Grolman for faster and simpler screening of IOP by optometrists. Briefly, an air-puff causes a transient applanation of the cornea, while an infrared light beam is reflected by the flattened surface. The amount of light reflected during the applanation period is compared with the time the air-puff took to cause applanation, allowing this device to provide an electronic measurement of the IOP. It also provides the ocular pulse amplitude (OPA) and tonographic measurements that estimate the aqueous outflow efficiency of the trabecular meshwork according to manufacturer information.

Modern non-contact tonometers have been found to correlate very well with GAT IOP, even though they tend to systematically overestimate IOP by 0.12–0.58 mmHg.(72–74)

Non contact tonometers are likely to be more influenced by CCT than GAT. In thinner corneas, there seems to better correlation between the tonometers, while in thicker corneas, non-contact tonometry systematically yields higher readings than GAT.(75) The device is less operator dependent and there is no risk of infection transmission. (72 -74)

G. Pneumato-tonometer (Mentor model 30, Classic Reichert, USA) c

This tonometer uses a pneumatic pump and a floating pneumatic sensor which touches the surface of the anesthetized cornea gently with the exact amount of applanation force

required to take the measurement. The air puff causes a transient applanation of the cornea and the infrared beam is reflected by the flattened surface. The amount of light reflected during the applanation period is compared with the time the air puff took to cause applanation. It provides real time readings of IOP through a non invasive applanation method. It can be used to measure IOP in contact-lenses wearers.(76) It significantly underestimates GAT measurements at lower IOP and overestimates these at higher IOP.(77) For example, for GAT IOP measurements <10 mmHg, the difference is around 2.0 mmHg, while for GAT IOPs ≥25, the difference is 0.6 (GAT - pneumotonometer et al). Also, as the GAT values increase, the pneumatonometer increasingly overestimates IOP.(77) In eyes with keratoconus, the pneumatonometer underestimates IOP by about 1.5 mmHg lower than GAT.(14) Similar to the air-puff tonometer, this device is a screening tool which can be easily used by non-specialized personnel.

Non Applanation Tonometry Devices

A. Dynamic Contour Tonometry - Pascal Tonometer (SMT, Swiss Microtechnology AG, Zurich, Switzerland

DCT is a relatively new digital tonometer, mounted on the slit-lamp and uses the principle of contour matching instead of applanation. The tip of the tonometer has a concave surface and allows the cornea to maintain its natural shape; when pressure on both sides are equal and corneal distortion is minimal.

The instrument has a concave tip with a diameter of 7 mm and radius of curvature of 7.5mm. When the probe is placed on the pre-corneal tear film on the central cornea the IOP is automatically measured 100 times per second. The tonometer tip applies a constant

appositional force of one gram on the cornea and when the piezo-resistive pressure sensor is subjected to a change in pressure, the electrical resistance is altered and the tonometer's computer calculates a change in the pressure according to a change in the resistance. The DCT measures the diastolic intraocular pressure and the Ocular pulse amplitude (OPA). Addition of the diastolic IOP to the OPA gives the value of systolic IOP. (Diastolic IOP + OPA= systolic IOP).

The OPA represents the average difference between the systolic and diastolic IOP within 6 heart beats. The OPA provides an alternate measure of the ocular blood flow.(78)

The DCT is said to be largely independent on the structural properties of the cornea and give an IOP recording which is closer to the true IOP.(11,13,79)

Many studies have shown that the DCT gives an accurate recording in patients with keratoconus,(14–16) corneal edema (17), post penetrating keratoplasty(11,15,80) and refractive surgery.(29,50) The DCT provides a quality check score (Q) and it ranges from 1 which is the optimum value to 5 which is unacceptable. For clinical and research purposes a score of 1 or 2 is considered reliable according to the manufacturer's information.

Most of the studies are on agreement that DCT tends to overestimate GAT by about 2.3 -3.4 mmHg, depending on the IOP level, CCT and other corneal properties.(11,13,50,60) Milla et al(81) found an optimal agreement between DCT and GAT when the CCT was between 540 and 545 μm. As the CCT and the IOP increased, the difference between both tonometers also increased.(60)

In eyes with keratoconus, the difference between DCT and GAT ranged from 4.3 to 5.3 mmHg with DCT recording higher values than GAT.(9,14,16) DCT seems to be largely independent of CCT in those patients. In eyes that had undergone keratoplasty and refractive surgery, DCT seems to be less influenced by changes in corneal properties following these procedures.(29,82,83) As a digital tonometer with an automated IOP quality check, together

with the increasing evidence of being largely independent of corneal properties, tonometry with DCT is a promising tool in clinical practice.

B. Tonometry-I care tonometer (Tiolat, Helsinki Finland)

This contact tonometer is based on the rebound principle described by Dekking and Coster in 1967. It uses a light probe containing a permanent magnet that is launched towards the eye using a solenoid. The probe hits the eye and bounces back. The same solenoid, inside which moves the probe, is used to detect the movement and impact of the probe, because the moving magnet induces voltage in the solenoid. The motion parameters measured during impact are used to estimate the IOP.(84,85)

It is a handheld, portable tonometer that displays the IOP reading digitally and does not require topical anaesthesia. Following 6 measurements, the device automatically determines the mean pressure and the standard deviation. It can be easily used by the patient himself and by non-specialized personnel.

Recent reports about its accuracy have been conflicting. Van der Jagt and Jansonius(86) found that I-Care slightly overestimated GAT by 0.6 mmHg (mean difference between 0.0 and 1.2 mmHg) even though this was not significant. On the other hand, Nakamura et al(60,84,87–89) studying a population that ranged from normal subjects to ocular hypertensives and glaucoma patients found that I-Care overestimated IOP, as compared to GAT, by 1.40±4.29 mmHg, and that this disparity tended to increase along with corneal thickness. They suggested that corneal thickness could affect the duration of the impact of the rebound tonometer, causing an overestimation in thicker corneas.

Only few studies are available on its use on irregular corneas. Jóhannesson et al(90) found that, unlike with the Goldmann tonometer, corneal curvature was not correlated with IOP

measurements taken with the I-care tonometer. Measurements with I-Care should always be interpreted with regard to CCT when used in a clinical basis.

C. Phosphene Tonometry (Proview, Bausch & Lomb Pharmaceuticals, Inc., Tampa, Fla.)

The pressure phosphene tonometer (PPT) is a self-tonometry device that was first described in 1998(91). It uses the entoptic phenomenon of pressure phosphene to evaluate IOP.(92,93) The PPT is initially applied perpendicular to the eyeball through the partially closed eyelid and the applied pressure is increased gradually until the moment when the patient clearly perceives a dark circle with a ring of light around the outer circumference (well-formed phosphene).The device is then removed from the eyelid and IOP can be read from the dial.(92,93)

The PPT presents several advantages, as it is a non contact device which does not need to be applied on the cornea but on the lid so there is no need of a topical anaesthetic. It is not influenced by corneal biomechanical properties and can be used to measure patient-specific, diurnal variations/.(91–93) . It has also been reported to have good reproducibility when used by patientsits accuracy is controversial.(94)

To summarise various types of tonometers as listed above are available commercially each of them having their own specific advantages and disadvantages. In general these devices are clinically used for diagnosis and patient follow up and also as a screening tool.

The DCT and ORA are independent of corneal biomechanical properties and may be more useful in eyes with corneal abnormalities. Different studies have shown good reproducibility and repeatability with these devices.(95) These devices will be useful not just for a single

measurement but for a regular follow up of the same patient and to assess the reduction in IOP after treatment is started.

The GAT measurements however remain irreplaceable because most studies available evaluate efficacy of procedures and efficacy of anti-glaucoma drugs on the basis of GAT values. Hand held tonometers show a fairly good agreement with GAT except for PPT and are good devices for screening purposes. Tonopen with reduced surface area and ease of use is useful in uncooperative patients with irregular corneas where accuracy of measurement can be affected. Newer devices like the ORA and DCT provide information not only on IOP but ocular hysteresis also.

It has helped build all the available knowledge regarding aqueous humour dynamics and IOP monitoring and remains a module for comparing all other devices. Readings from newer IOP devices should not be interchanged even in the normals and the same device should be used by the clinician depending on which one suits best for a particular patient.

Among all available devices no single tonometer can provide IOP readings with high accuracy regardless of CCT or corneal irregularities. A customised application seems more reasonable.(10)

Summary of Tonometers

Tonometers	Portability	Accuracy Relative to GAT	Accuracy Irregular Corneas	Accuracy Corneal Thickness
GAT	-		-	-
Perkins	+	Good concordance	-	-
Tonopen	+	Depends on IOP level	-	-
ORA	-	Overstates	+	+
NCT	+/-	Depends on device model and IOP level	-	-
DCT	-	Overstates	-	+
Pneumotonometer	+	Overstates	+	-
Phosphene Tonometer	+	Understates	+	+

Review of important studies

Studies in normal patients

In a prospective study by Kauffmann et al comparing GAT and DCT in normal eyes (n=228), IOP measurements and analysis of the effects of CCT, corneal curvature, axial length, and anterior chamber depth was done. Intra- and inter observer variability was evaluated by measuring the IOP in 8 eyes by 4 observers. A high concordance was shown between the IOP readings obtained by DCT and GAT. However, IOP readings were persistantly higher with DCT than with GAT. Regression analysis showed no effect of the CCT and other factors on the DCT. They concluded that DCT IOP was highly acordant with GAT IOP readings but do not vary with variations in CCT and have a lower intra- and inter-observer variability. They concluded that DCT was an appropriate tonometer for routine clinical use.

Tonnu et al (n=105), measured IOP in patients with glaucoma and ocular hypertension using GAT, Tonopen, Ocular Blood flow Pneumotonometer (OFB), and Canon TX-10 non-contact tonometer (NCT). Independent observers took three IOP measurements with each instrument, and two with GAT. They obtained mean IOP differences of 0.4 mmHg between GAT observers, and 0.6 mmHg, 0.1 mmHg, and 0.7 mmHg between GAT and Tonopen, OBF, and NCT, respectively. A moderate inter-instrument concordance was shown between the NCT and GAT and poor concordance between the Tonopen and OBF with GAT. The differences between the GAT and OBF and between GAT and Tonopen, thereby probably interdicting the OBF and Tonopen from routine clinical use as objective tonometry methods to measure IOP in normal eyes.

Geyer et al (n=82) compared the Oculab tonopen with GAT in normal eyes and found that 48% of eyes showed different IOP values with the GAT and tonopen Mean difference of (-3,

59 (SD 0.36). They showed a correlation (r =0.83) in normal eyes, but tonopen overestimated the IOP ($p<0.001$) in these eyes. They concluded that the tonopen consistently overestimated the IOP in an unpredictable pattern.

Studies in Keratoconus

In a prospective study by Papastergiou et al (n=156), IOP measurements in keratoconus (n=64) was compared with age matched controls using GAT, DCT, and the NCT. In the control group (n=92), an interrelation between DCT, GAT, and NCT IOP measurements was noted. In keratoconus, GAT and NCT IOP measurements were incomparably lower than DCT measurements (5.3 ± 2.2 mmHg and 4.75 ± 1.7 mmHg, respectively). DCT IOP in both groups was not significantly affected by CCT.

In a prospective study by Mollan et al, IOP was measured in a random order using GAT, DCT, ORA and Tonopen XL in normal (n=92) and keratoconus (n= 64). CH and corneal resistance factor (CRF) which was calculated by the ORA were recorded. The difference in IOP values between instruments was greatly significant in both groups ($p<0.001$). It was seen that the Tonopen, although relatively independent of the CCT, CH and CRF had a tendency to overestimate IOP when compared with GAT in both normal and keratoconus eyes. The DCT showed no inclination compared to mean IOP measurements and was not affected by CCT and CH, however, the IOP values obtained were higher than with GAT. IOPg and IOPcc which were measured by the ORA were found to be suitable when compared to the GAT in the control group and keratoconus group, respectively. IOPcc showed relative independence from CCT and CRF. They concluded that DCT and ORA are possibly the most accurate tonometers to use in Keratoconus currently.

Schadle et al, measured IOP in 114 eyes with keratoconus using GAT and DCT in a randomized order. The Pentacam recorded the CCT, minimal corneal thickness (MCT), and corneal topography. In all the four groups of keratoconus with variable CCT and MCT values, depending on the grade of Amsler's classification were evaluated. The study showed that DCT IOP was higher than GAT IOP (mean difference 1.6 ± 2.6 mmHg). In keratoconus, both methods seem to be independent of CCT and therefore are equally, but not interchangeably, applicable when monitoring IOP. They concluded that both GAT and the DCT are equally suitable for determination of IOP in keratoconus which are independent of the thickness of the cornea. However, for clinical monitoring one should always use the same measurement techniques since the DCT measures approximately 1.6 mmHg higher pressures as compared to GAT. Further analysis revealed that the CCT and MCT were notably different in corneas of different Amsler grade

Meyenberg et al compared DCT with GAT in 30 eyes with keratoconus and 29 eyes following Penetrating Keratoplasty (PK). GAT and DCT IOP values were taken in these eyes after pachymetry and corneal topography. DCT IOP was significantly higher than GAT IOP in both study groups (4.1 ± 2.3 mmHg in keratoconus and +3.1 ± 2.5 mm Hg after PK.) In comparison to DCT, GAT IOP was significantly higher in PK eyes than in keratoconus. The correlation between the two tonometry methods was moderate in both groups. In the keratoconus group, it was seen that DCT gave a significantly higher IOP value than GAT in both groups. IOP measured with DCT and GAT showed a considerable variation, however DCT was not completely independent of biomechanical properties of irregular corneas than when compared to GAT.

Browning AC et al (n =127), compared IOP measurements using GAT, Tonopen and the OBF pneumotonometer in eyes with varying CCT such as keratoconus (n= 37), penetrating keratoplasty (n=56) and Fuch’s endothelial dystrophy (FED) (n= 34). Mean IOP values in all

three patient groups were significantly higher when measured by OBF pneumotonometer. A Linear regression analysis was done which showed that patients with FED had a significant increase in IOP with increasing CCT of 0.18 mm Hg/10μ using GAT, 0.15mmHg/10μ with the tonopen, and 0.26 mmHg/10μ with the OBF pneumotonometer. In patients with Keratoconus and after PK, linear regression analysis did not reveal any significant consequence of CCT on IOP. A multivariate linear regression model controlling for age, sex, graft size, and patient group, showed that the effect of CCT on Tonopen IOP (0.13 mm Hg/10 μ CCT) and GAT (0.14 mm Hg/10 μ CCT) were significantly lesser than for the OBF pneumotonometer (0.26 mm Hg/10 μ CCT) They found that the mean IOP values using the OBF pneumotonometer were significantly higher than those made using the GAT or Tonopen in all these corneal pathologies. The OBF pneumotonometer was found to be most afflicted by alteration in CCT. For all three instruments, the affinity between IOP and CCT depended on the corneal pathology and was immense in FED.

Jackson Barreto et al compared DCT with GAT in 10 keratoconus patients and 12 normals. It was found that the DCT readings were higher than GAT in keratoconic patients but lower than the DCT readings in the control group. The dissemblance between both methods was statistically significant in keratoconus ($P < 0.0002$) This may have been probably due to discrepancy between the radius of corneal curvature in keratoconus and the DCT tip, the significant thinning of these corneas, or other corneal biomechanical abnormalities like abnormal hysteresis.

A prospective study was done by Zeynep Ozbek et al on patients with keratoconus with and without PK and pellucid marginal degeneration (PMD) eyes comparing the IOP using three different tonometers viz. DCT, GAT and Tonopen. A total of 53 eyes of 36 patients were

enlisted in the study which included 29 eyes of patients with keratoconus, 21 eyes after PK for keratoconus and 3 eyes with PMD. Severity of ectasia was determined by videokeratography and ultrasound pachymetry. Mean GAT, DCT and Tonopen IOP were 14.3 ± 4.1, 16.1 ± 2.9 and 13.8 ± 4.1 mm Hg, respectively. The differences of mean IOP values between GAT and DCT and Tonopen and DCT were statistically significant, whereas the difference between GAT and Tonopen was not. Both GAT and Tonopen IOP values were significantly higher in the PK eyes than the KC and PMD eyes, whereas DCT IOP value was not. DCT values were not significantly different in PK versus non-PK eyes It was found that DCT provided a higher IOP than Tonopen and GAT in both keratoconus and PMD and DCT gave the same values in both conditions. The DCT IOP was not influenced by the CCT which will probably make it more reliable in measuring IOP in patients with keratoconus and PMD

According to a prospective comparative study done by Scott and Collins in comparing DCT and NCT in 20 keratoconus patients and 20 age matched controls. The average DCT IOP value was 14.2 ± 1.4 mm Hg in keratoconus and 14.2 ± 1.6 mmHg in controls. However, the average NCT readings diverged significantly ($p < 0.001$) amidst the keratoconus group (9.2 ± 1.5 mmHg) and the controls (12.9 ± 2.4 mmHg). IOP measurements taken with the DCT showed no significant ($p > 0.05$) concordance with the severity of keratoconus as resolved through measures of Videokeratography and pachymetry. Corresponding IOP measurements taken with the NCT correlated significantly with measures of corneal curvature and thickness in the keratoconus group. They found that there was no significant difference between the DCT IOP measured between keratoconus and aged matched controls; and also the DCT was independent of the CCT. The DCT provided dependable IOP values in patients with keratoconus as compared to NCT It was found that they were similar to the aged matched

controls and independent of the biomechanical properties of cornea, where as NCT appeared to be dependent on corneal biomechanical properties

.

In a prospective study by Attila Bayer et al; to determine the agreement between DCT, GAT, and ORA in keratoconus and the effect of corneal biomechanics on IOP values obtained by these devices. IOP values were obtained with the ORA, DCT, and GAT in random order in one hundred twenty eyes of sixty keratoconus patients after they underwent a BCVA, slit lamp biomicroscope examination and corneal topography. The mean CCT obtained was 464.08 ± 58.4µ. The mean difference between IOPcc and GAT, IOPcc and DCT, GAT and DCT, IOPg and GAT and IOPg and DCT was greatly statistically significant. A multivariate regression analysis showed DCT IOP and GAT IOP values were significantly associated with CH and CRF ($P<0.0001$) for both groups and it was found that DCT seemed to be dependent on CH and CRF and DCT IOP tended to be higher in comparison to GAT IOP. ORA measured IOPcc and this value was not dependent on the CCT and was in contrast to the IOP measured with DCT in keratoconus.

A prospective study was done by S.Patel et al to measure and compare CCT and IOP in keratoconic and post-keratoplasty eyes and observe the CCT-IOP relationship. 22 keratoconus and 19 post keratoplasty subjects were enrolled. The mean values for CCT and IOP in keratoconus and keratoplasty eyes were: 445 ± 45µ and 9.8 ± 2.3 mmHg, 564 ± 44µ and 15.8 ± 3.9 mmHg respectively. Differences between both groups were significant for CCT as well as IOP ($p=0.01$). Within each category, a significant concordance between CCT and IOP was not found ($p =0.001$). These results confirm the hypothesis that a higher IOP is measured in an eye with a thicker cornea.

MATERIALS & METHODS

Materials and Methods

Study Design

This is a case control study conducted in the department of Ophthalmology, Christian Medical College Vellore from August 2013 – September 2014.

Study population

Cases: Patients with keratoconus who are recruited from the outpatient department of the department of Ophthalmology, Christian Medical College, Vellore.

Controls: Normal patients who are recruited from the outpatient department of the department of Ophthalmology, Christian Medical College, Vellore.

Inclusion criteria for Cases/Keratoconus

Keratoconus was diagnosed based on any one or more of the following signs.

External signs; Rizzuti's sign, Munson's sign,

- Scissoring reflex on retinoscopy
- Slit lamp findings of Fleicher's ring or Vogts striae or corneal thinning and
- confirmed by Videokeratography criteria such as an axial topography consistent with keratoconus with a flat keratometry reading more than 51D, Keratoconus Prediction Index (KPI) > 0.23, Differential Sector Index (DSI)> 2.4, Opposite Sector Index (OSI)> 2.0 and Centre Surround Index (CSI) >1.25 (Klyce/Maeda). (KPI > 0.23, DSI > 2.4 and CSI > 2.0)

Inclusion Criteria for normals (controls)

Normal individuals were defined as

- Age less than 40 years
- Emmetropes, myopes, hyperopes and regular astigmatism upto 2D
- No ocular pathology seen on slit lamp examination
- Regular axial topography pattern (round, oval or symmetric bow tie)
- Average corneal power < 47.5D & flat Keratometry> 38.50D
- Keratoconus Prediction Index less than 0.23as recorded by videokeratography.

Exclusion criteria for cases and controls

- Corneal epithelial defects, scarring and oedema,
- Uveitis,
- Un-cooperative patients,
- Presence of nystagmus
- DCT fails to give a quality factor of 1 or 2 after 3 attempts

Institutional Review Board

The study protocol was approved by the institutional review board and ethics committee of Christian Medical College, Vellore as per the ICMR guidelines required for any study to be conducted in the institution. The IRB clearance was obtained on 26th August, 2013

Methodology

This is a prospective comparative case series.

Among patients attending the out-patient department of Ophthalmology, Christian Medical College, Vellore patients diagnosed as keratoconus and as normals underwent a videokeratography (TOMEY, topographic modelling system IV, Japan). Those satisfying clinical and videographic criteria (ANNEXURE VI) for cases and controls were invited for the study. The study procedure was explained to the patients.

Those agreeing to participate in the study were recruited into the study after signing the informed consent. All the IOP recordings were done by the principal investigator.

After topical application of a local anaesthetic Paracain (Proparacaine hydrochloride 0.5%), first the IOP was measured with the Goldmann Applanation Tonometer (GAT), (Haag Streit, Koeniz, Switzerland), 2 recordings were taken in both eyes within a period of 1 minute ; in keratoconus patients the two readings were taken with one in the axis of astigmatism and the other 90 degrees opposite to it in a period of 1 minute. The second method of measurement of IOP was with the Dynamic Contour Tonometry (DCT) (PASCAL, Ziemer Switzerland); 2 readings were obtained from both eyes, with quality factor of 1 or 2, the second reading was taken after 2-3 minutes. The third method of measurement of IOP was with a Tonopen AVIA (Reichert, Buffalo NY) and 2 consecutive recordings with 5% standard deviation within a period of 1 minute were obtained from both eyes. As the DCT and tonopen provided a readout on liquid crystal display, prior knowledge of the GAT result would not influence the result and made it unnecessary to randomize the IOP measurements, but however the investigator was masked to the results.

In all the above mentioned methods, the average of the two readings was used for analysis.

The principal IOP recordings (values) were noted down by an optometry student/intern so as to prevent bias. The tests were repeated after one hour to look for the reproducibility of IOP with these instruments. Following recording of intraocular pressures, the central corneal thickness was recorded in all recruits using an ultrasound pachymeter (SP -100, TOMEY, USA) by an experienced optometrist.

Statistical Analysis of Data

Data analysis was done with Excel (Microsoft Corporation, Redmond, USA) and SPSS (SPSS Inc., Chicago, Illinois, USA). Linear regression analysis was done and r^2 was calculated to find the power. Pressure differences between the three tonometers were analysed using the Wilcoxon signed rank test. Spearman's correlations were used to assess the dependence of the tonometers on CCT as well as to assess reproducibility. Bland–Altman plots were constructed for comparisons between different tonometer techniques. ANOVA was used to compare values obtained by the tonometers.

Sample Size Calculation

Sample size calculation was based on the desired precision of Intraclass Correlation (ICC).

The desired lower limit of 0.50 for ICC's of 0.70, 0.65 and 0.60 (interval widths of 0.40, 0.30 and 0.20 respectively) for 3 measurements require 67, 149 and 398 respectively. We decided to aim for a total sample size of 100. This sample size would also meet the requirements for the Bland- Altman analysis

	ICC	Prescision	Confidence Interval	Sample Size
1.	0.70	0.20	95%	67
2.	0.65	0.15	95%	149
3.	0.60	0.10	95%	398

In view of comparison between the two groups a sample size of 100 in each group was arrived at.

Software used for Data Analysis: STATA

RESULTS

Results

A total of 173 eyes of 141 patients were evaluated and included in the study. Two groups of patients were studied. There were 73 eyes from 41 keratoconus patients (cases) and 100 eyes of 100 normal patients (controls) included in the study.

Demographic Profile

Their demographic profile is shown in table 1 and 2

Table1: Demographic Profile of all patients

Total Patients	**141**
Male	49 (34.75%)
Female	92 (65.24%)
Age	10-52 (years)
Mean Age ± Standard Deviation	23.3 (years) ± 6.40

Table 2: Demographic Profile of cases and controls (N=141)

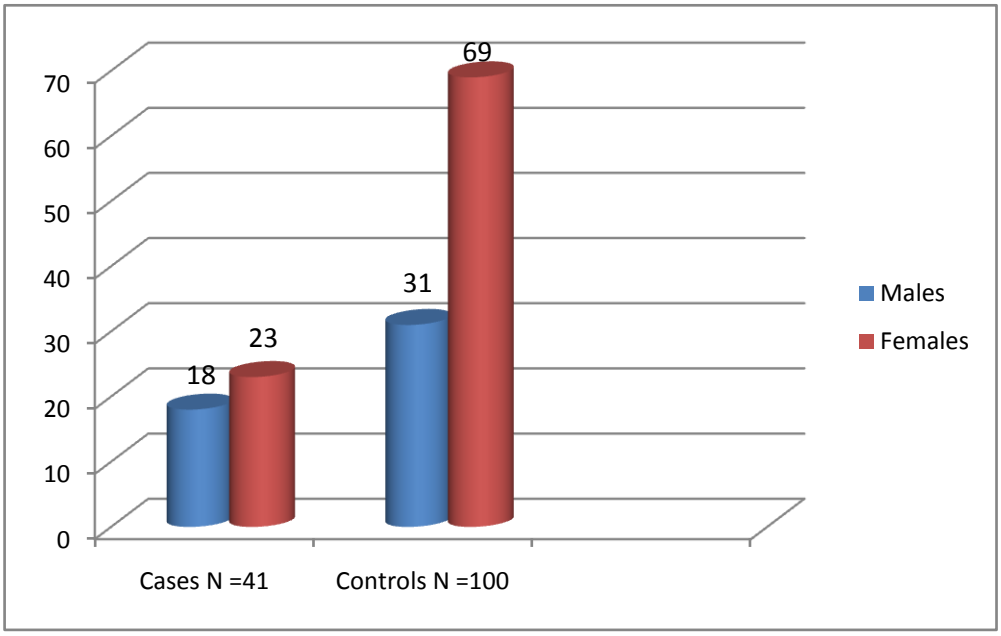
Patients	**Cases (n=41)**	**Controls (n=100)**
Male	18 (43.90%)	31 (31%)
Female	23 (56.09%)	69 (69%)
Age	10-52 (years)	13-38 (years)
Mean Age ± Standard Deviation	22.3 (years) ± 8.1	24.4 (years) ± 4.49

56.09 % of the cases were females and the age ranged from 10 to 52 years. 69% of the controls were females and the age range was from 13 to 38 years.

Gender Distribution

The graph below depicts the gender distribution of our study population.

Figure 1: Gender distribution in cases and controls



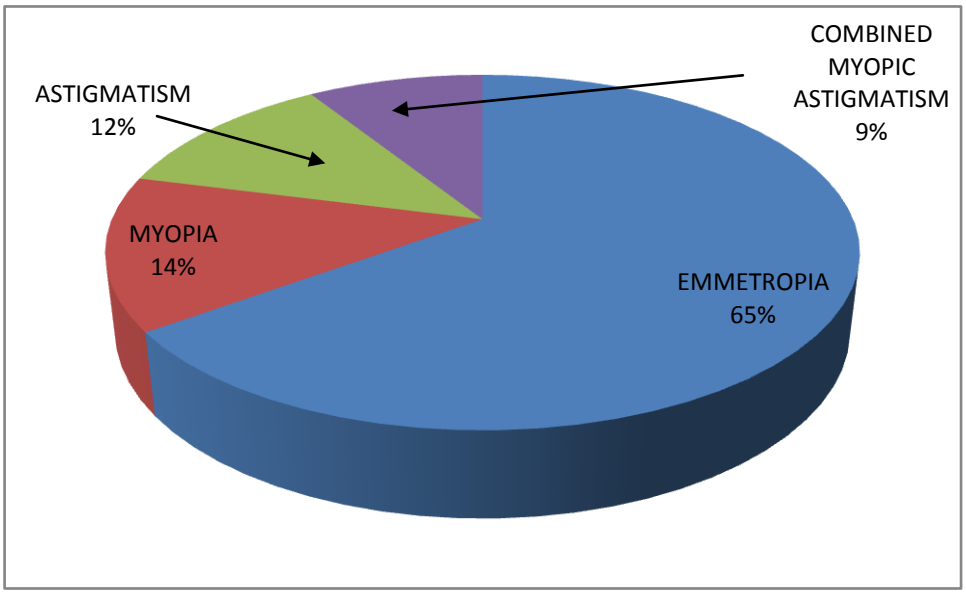
Majority of the participants in our study population were females

Refractive errors in control group

We studied the distribution of refractive errors among controls

Distribution of refractive errors among controls as shown in Figure 2

Figure 2 **Distribution of refractive error among controls**

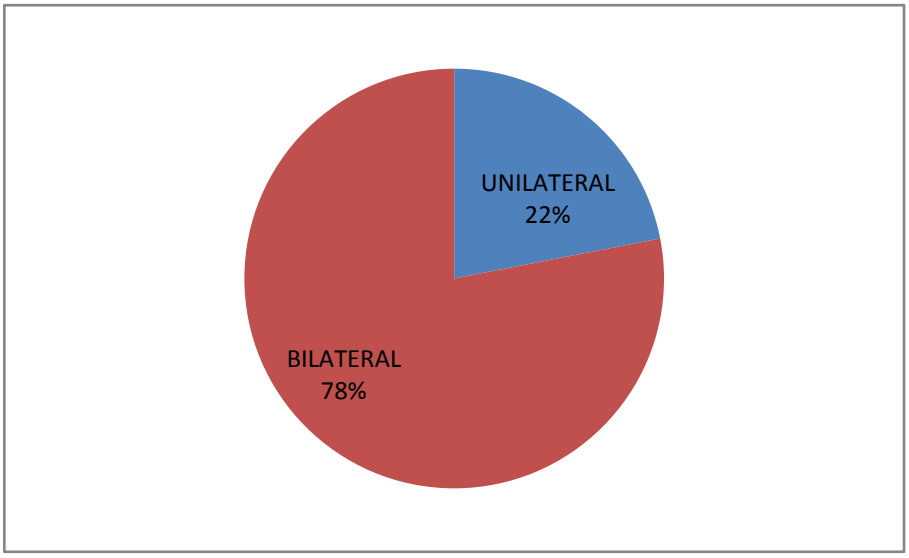


In the control group 65% of eyes had emmetropia

Laterality among Keratoconus

The number of patients who had unilateral or bilateral keratoconus is depicted in figure 3

Figure 3 Unilateral vs Bilateral (n=41)



78% of the cases had bilateral keratoconus

Keratometry Reading

We studied the minimum or the flat keratometry readings of the cases and controls and they are given in Table 3

Table 3 Flat Keratometry Reading

Patient	**Keratoconus**	**Controls**
Mean Flat K ± SD	53.18 D ± 5.47	44.61D ± 1.5
Range	43.47 D – 67.40D.	41.37 D –47.48D

Flat keratometry reading ranged from 43.47 to 67.40 D among the keratoconus

Signs of Keratoconus

We looked at the classical described signs of keratoconus in our patients and they are described in table 4

Table 4 Signs of Keratoconus

Signs of Keratoconus	**No of eyes**
Munson's sign	38
Vogt's striae	54
Fleicher's Ring	47

Vogt's striae was seen in 54 eyes

Intraocular Pressure (IOP) measurements

We studied the distribution of the IOP measurements with the three different tonometers in keratoconus and the results are shown in table 5

Table 5 IOP in keratoconus with GAT, DCT & Tonopen

Tonometer	Mean IOP (mmHg) ± SD	Range (mmHg)
Goldmann Applanation Tonometer	12.06 ± 2.12	8-16
Dynamic Contour Tonometer	14.83 ± 2.49	10-21
Tonopen	12.34 ± 1.88	8-17

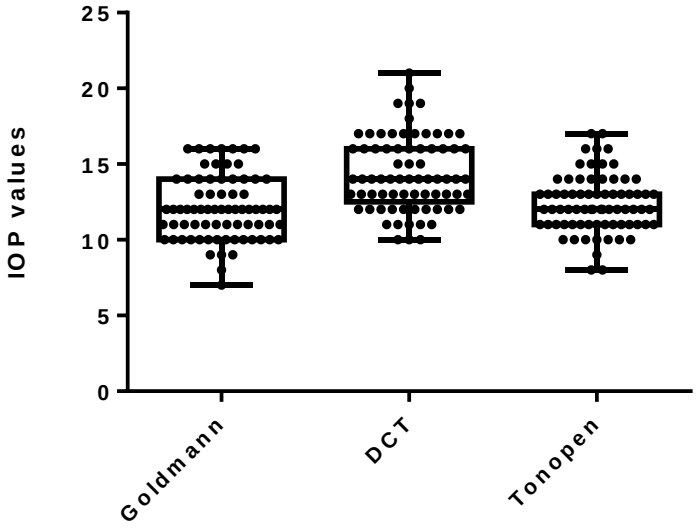
The IOP measured with DCT was noted to be higher than with GAT and Tonopen in keratoconus

Box and Whisker plot

The box and whisker plot shows the mean and range of IOP as obtained by the various tonometers among normals and keratoconus

The IOP distribution in keratoconus as obtained by GAT, DCT and Tonopen is shown in Figure 4.

Figure 4 Box and Whisker plot of IOP distribution in keratoconus



In keratoconus the 50th percentile was 12mm Hg for GAT, 14mm Hg for DCT and 12mm Hg for tonopen.

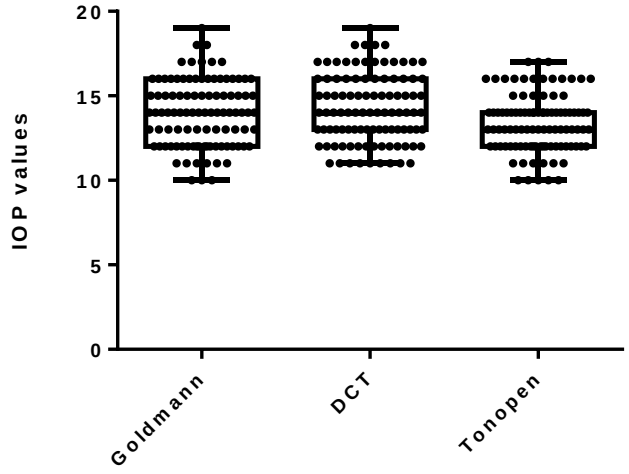
The distribution of IOP measurements with the three different tonometers among normals are shown in table 6

Table 6 IOP in control group

Tonometer	**Mean IOP (mmHg) ± SD**	**Range (mmHg)**
Goldmann Applanation Tonometer	13.94 ± 1.96	10-19
Dynamic Contour Tonometer	14.22 ± 2.04	11 -19
Tonopen	13.36 ± 1.70	10-17

The IOP distribution among controls using the box and whisker plot is shown in Figure 5

Figure 5 Box and Whisker plot of IOP distribution in control Eyes



In the control group the 50th percentile was 14mm Hg for GAT, 14mm Hg for DCT and 13mm Hg for Tonopen.

Intraocular Pressure difference

We analysed the mean difference in IOP between the various tonometers in patients with keratoconus and normals and the results are shown in table 7

Table 7 Mean Difference in IOP between cases and controls

Tonometers	Keratoconus (mmHg)	Controls (mmHg)
GAT IOP –DCT IOP	-2.32	-0.27
GAT IOP –Tonopen IOP	-0.27	0.58
DCT IOP – Tonopen IOP	2.04	0.82

The mean difference in IOP between the tonometers was different for keratoconus and controls and this was shown to be statistically significant, p value < 0.001

Intraclass correlation coefficient (ICC)

We analysed the ICC for the three tonometers in both cases and controls and the results are shown in table 8

Table 8 Intraclass Correlation between tonometers in cases and controls

Tonometers	ICC (keratoconus) with 95% CI	P value	ICC (controls) with 95% CI	P value
GAT -DCT	0.62 (-0.09 – 0.84)	<0.001	0.64 (0.42 -0.77)	<0.001
GAT-Tonopen	0.83 (0.73 -0.89)	<0.001	0.81 (0.68 – 0.88)	<0.001
DCT-Tonopen	0.51 (0.46 -0.61)	<0.001	0.59 (0.25 -0.57)	<0.001

In both keratoconus and controls a fair to good agreement was shown between GAT and DCT, an excellent agreement between Tonopen and GAT and a fair agreement between DCT and Tonopen

Mean IOP

We analysed the median IOP with the three tonometers among keratoconus and controls and the results are given in Table 9

Table 9 Mean IOP in Keratoconus and controls

	Keratoconus		Controls	
Tonometers	Mean ± SD	Median ± SD	Mean	Median
GAT	12.06 ± 2.12	12	13.94 ± 1.96	14
DCT	14.83 ± 2.49	14	14.22 ± 2.04	14
Tonopen	12.34 ± 1.88	12	13.36 ± 1.70	13

The median (inter quartile range [IQR]) of GAT IOP among keratoconus was 12 (10 -14). Similarly the median (IQR) of GAT IOP among controls was 14 (12 -16). There was a statistical significant difference in the median GAT IOP values among cases and controls (p value< 0.001).

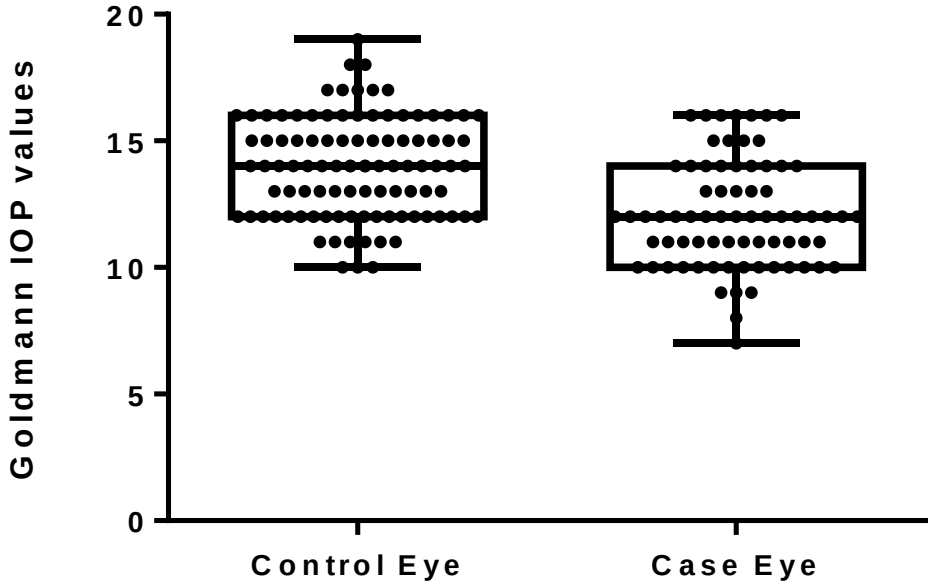
The median (IQR) of DCT IOP among keratoconus was 14 (12 -16). Similarly the median (IQR) of DCT IOP among controls was 14 (12 -16). There was no statistical significant difference in the median DCT IOP values among cases and controls (p value = 0.80

The median (IQR) of Tonopen IOP among keratoconus was 12 (11 -13). Similarly the median (IQR) of Tonopen IOP among controls was 13 (12 -14). There was a statistical significant difference in the median Tonopen IOP values among cases and controls (p value< 0.001). *There was a statistical significant difference in the median Tonopen IOP values among keratoconus and controls (p value< 0.001).*

Box and Whisker plot of IOP distribution

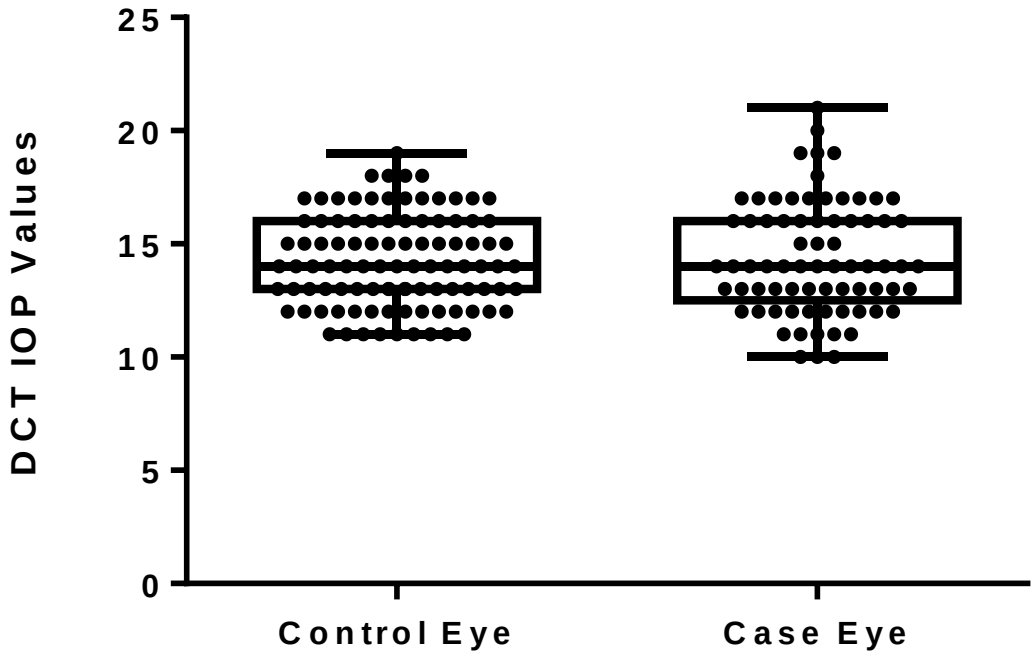
The IOP distribution with GAT, DCT and Tonopen among keratoconus and controls using the Box and Whisker plot are given in Figures 6, 7 and 8.

Figure 6 Box and Whisker plot of IOP distribution with GAT among keratoconus and controls



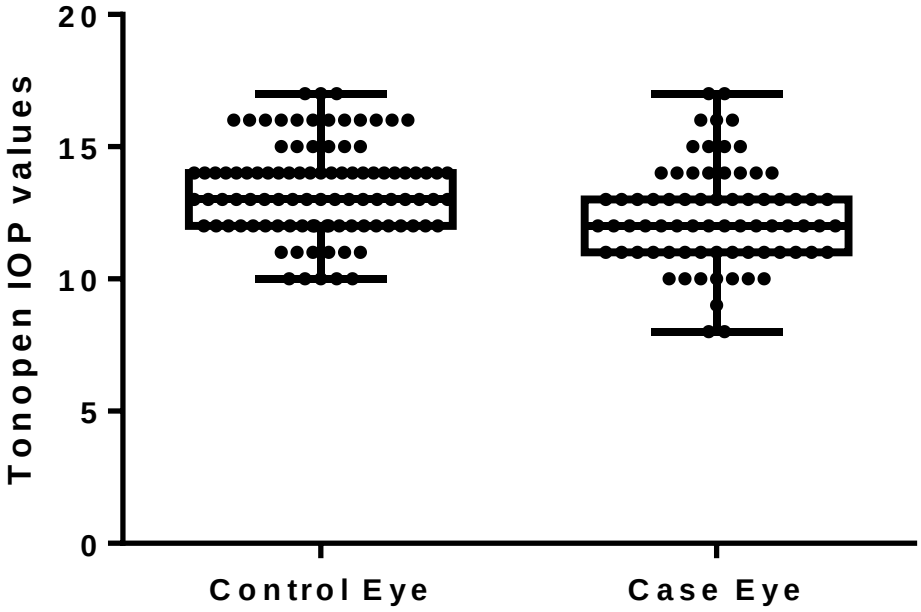
The GAT IOP values were higher in the controls than those obtained in keratoconus.

Figure 7 Box and Whisker plot showing IOP distribution with DCT among keratoconus and controls



The DCT IOP values were similar in keratoconus as well as controls

Figure 8 Box and Whisker plot of IOP distribution with Tonopen among keratoconus and controls



The Tonopen IOP values were slightly less in keratoconus than in controls.

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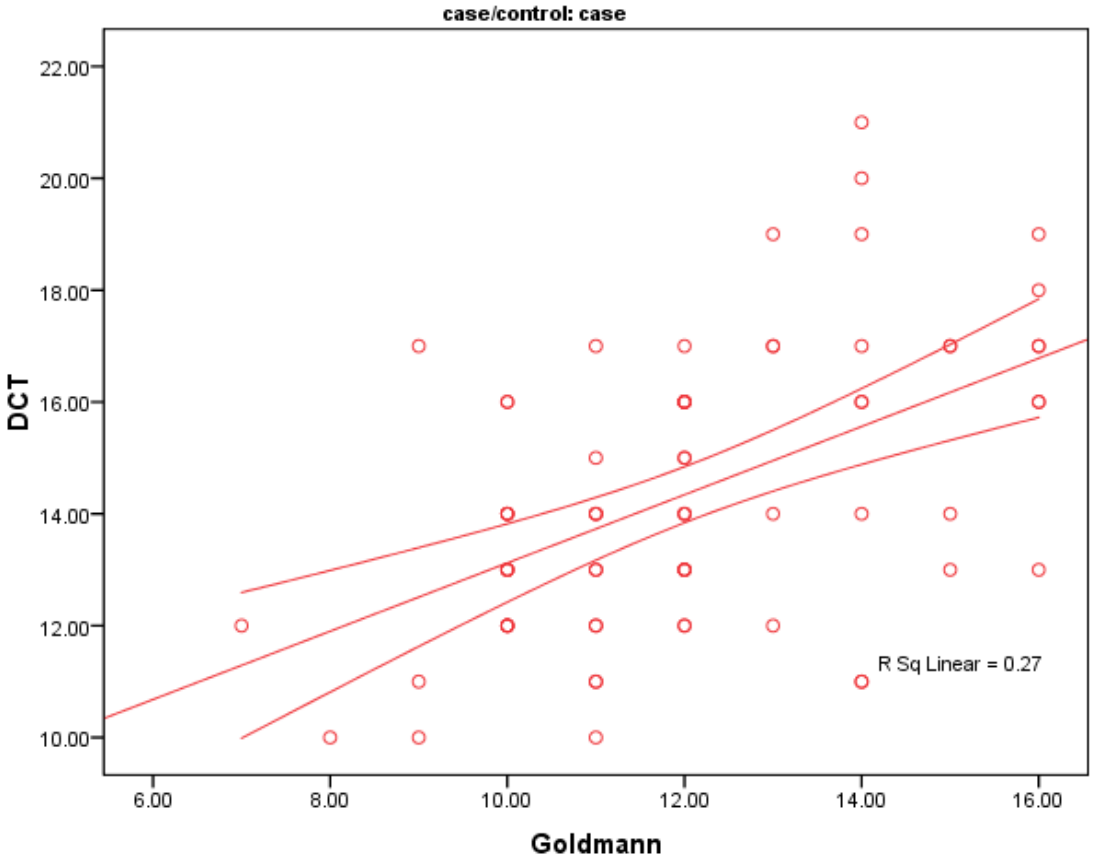
Correlation analysis of IOP measurements

Figure 9 shows the correlation analysis of IOP measurements (mm Hg) when taken with DCT and GAT in keratoconus eyes. The Univariate Linear Regression analysis method was used and the correlation was statistically significant ($r^2 = 0.27$, $P < 0.001$).

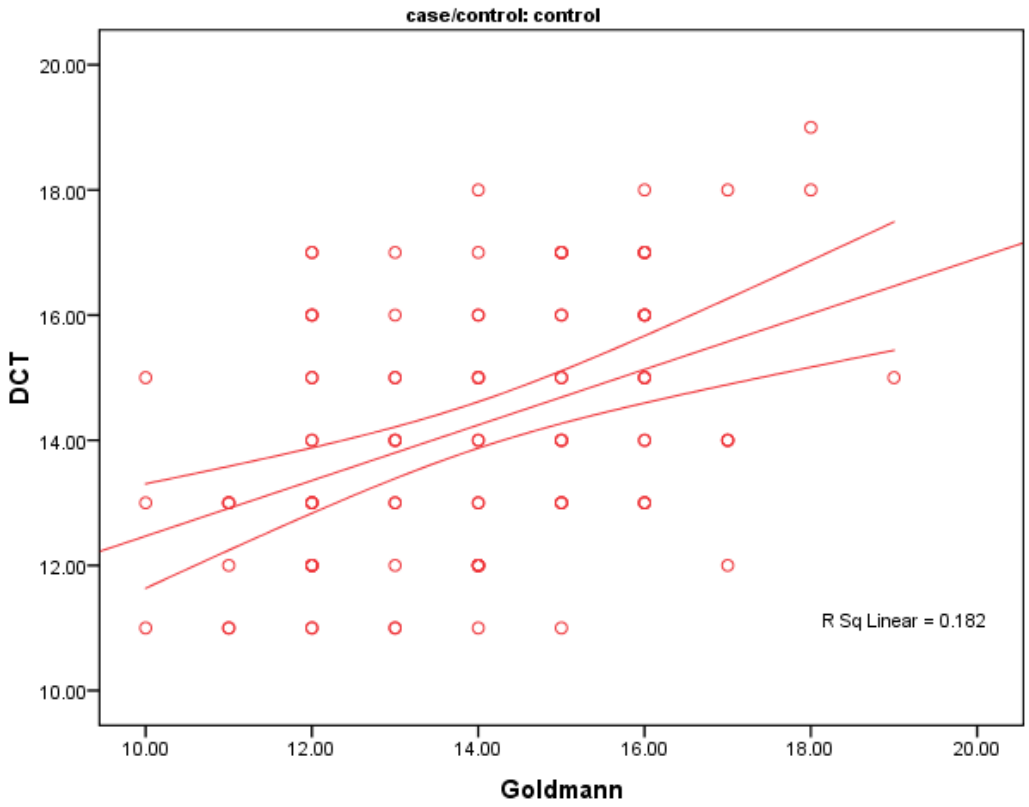
Figure 9 Scatter plot of GAT and DCT along with Best Fit line and its 95% CI



In the regression analysis in keratoconus group between DCT and GAT, it was shown that for every 1 mmHg rise of IOP with the Goldman applanation tonometer there was a 0.60mmHg rise of IOP with the DCT. The GAT values correlated well with DCT in the keratoconic eyes and the difference was statistically significant ($p < 0.001$).

Figure 10 shows the correlation analysis of IOP measurements taken with DCT and GAT in the control group. The correlation was significant ($r^2 = 0.18$, $P < 0.001$).

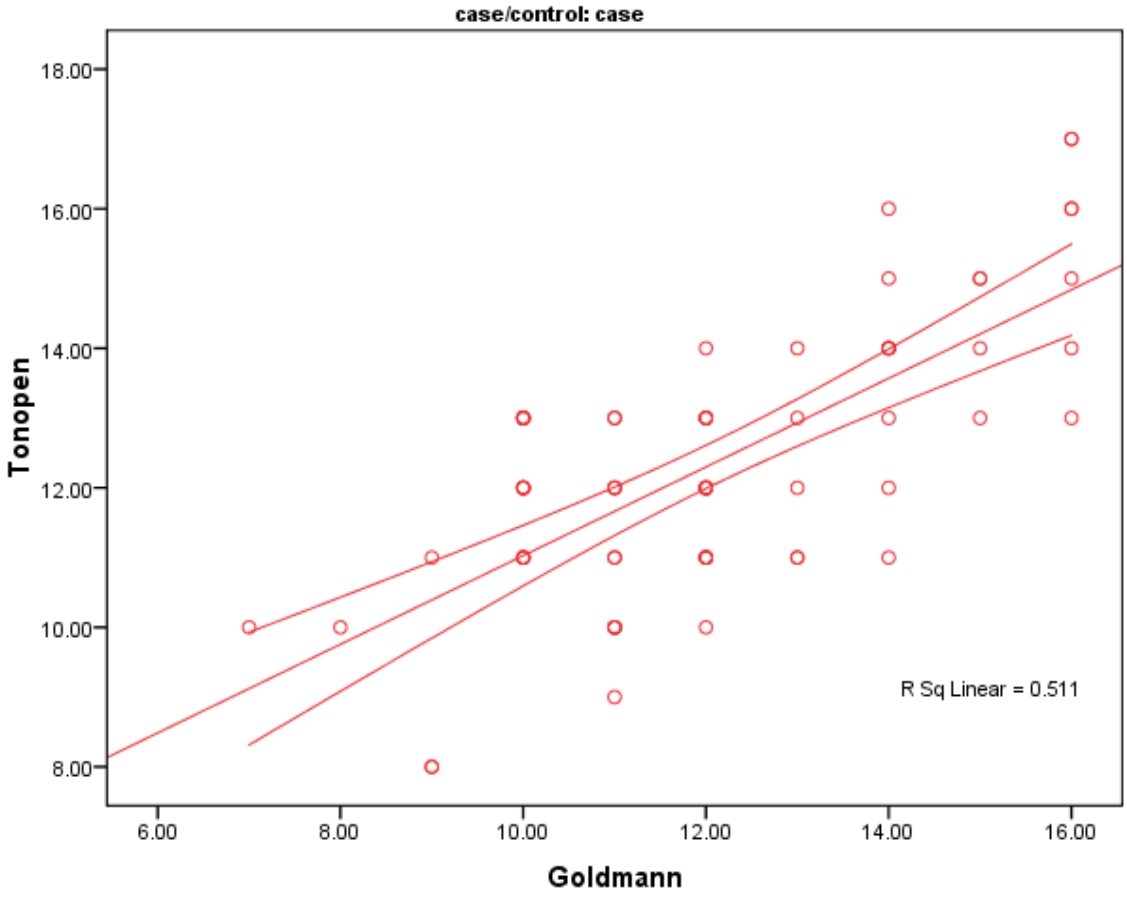
Figure 10 shows the scatter plot of GAT and DCT along with Best Fit line and its 95% CI



In the control group s the IOP increased by 1mm Hg with GAT there was an increase in 0.44mm Hg with the DCT, p < 0.001). The correlation between DCT and GAT was significant in the control group.

Figure 11 shows the correlation analysis of IOP measurements when taken with Tonopen and GAT in the keratoconus group. The correlation was significant ($r^2 = 0.51$, $P < 0.001$).

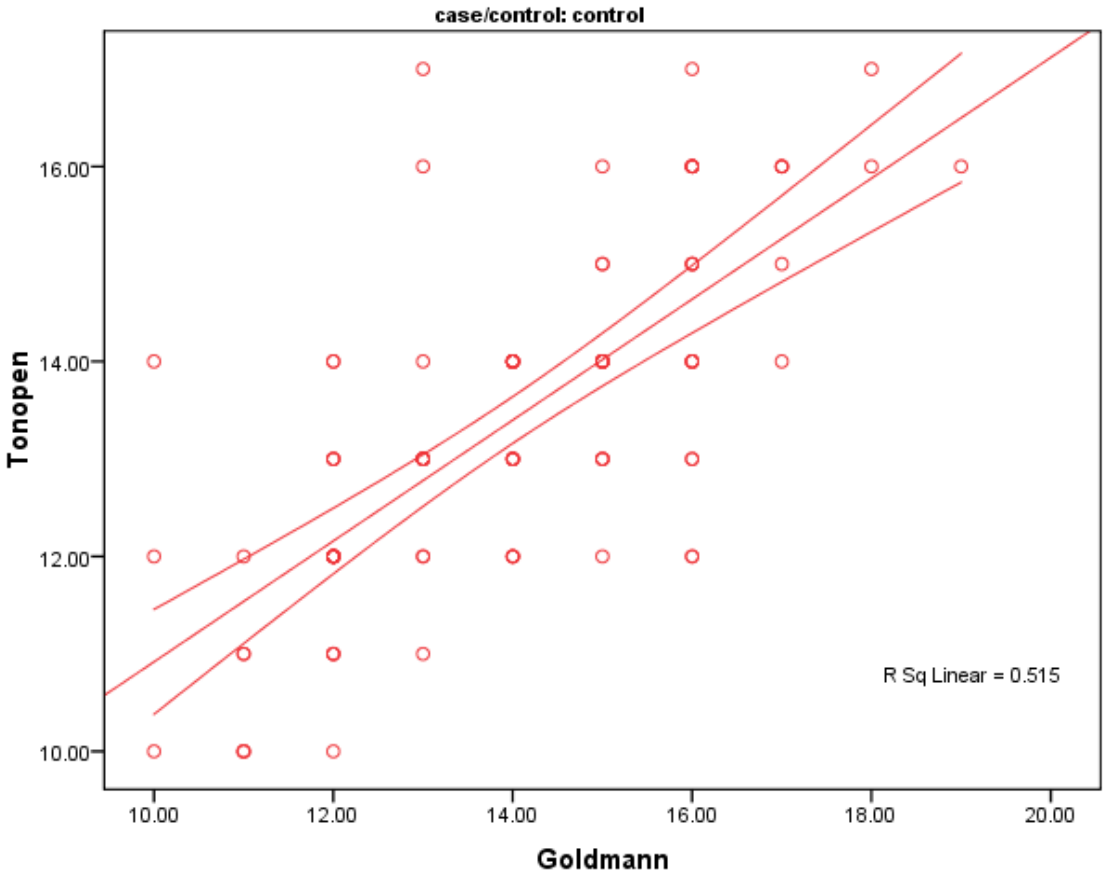
Figure 11 Scatter plot of Tonopen and GAT along with Best Fit line and its 95% CI



In the regression analysis between Tonopen and GAT in the keratoconus group, it was shown that as IOP measured with GAT increased by 1mmHg there was an increase in 0.63mmHg with the Tonopen ($p < 0.001$). The Tonopen and GAT IOP measurements correlated well in keratoconic eyes

Figure 12 shows the correlation analysis of IOP measurements when taken with Tonopen and GAT in the control group. The correlation was significant ($r^2 = 0.51$, $P < 0.001$).

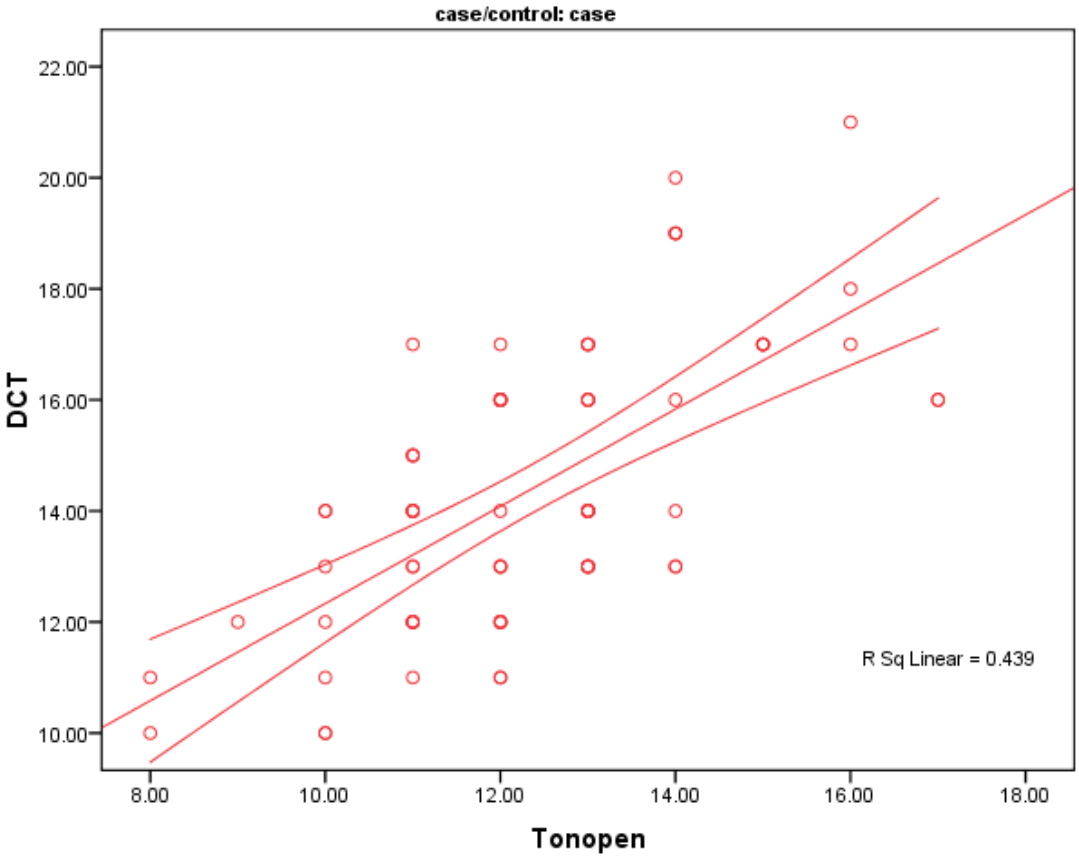
Figure 12 Scatter plot of Tonopen and GAT along with Best Fit line and its 95% CI



In the regression analysis between Tonopen and GAT in the control group, , it was shown that as IOP measured with GAT increased by 1mmHg there was an increase in 0.62mmHg with the Tonopen ($p < 0.001$). The Tonopen and GAT IOP measurements correlated well in the controls.

Figure 13 shows the correlation analysis of IOP measurements when taken with DCT and Tonopen in keratoconus group. The correlation was significant ($r^2 = 0.43$, $P < 0.001$).

Figure 13 Scatter plot of DCT and Tonopen along with Best Fit line and its 95% CI



In the regression analysis between DCT and Tonopen in the keratoconus group, it was shown that as IOP measured with Tonopen increased by 1mmHg there was an increase in 0.87mmHg with the DCT. The DCT and Tonopen IOP measurements correlated well in keratoconic eyes.

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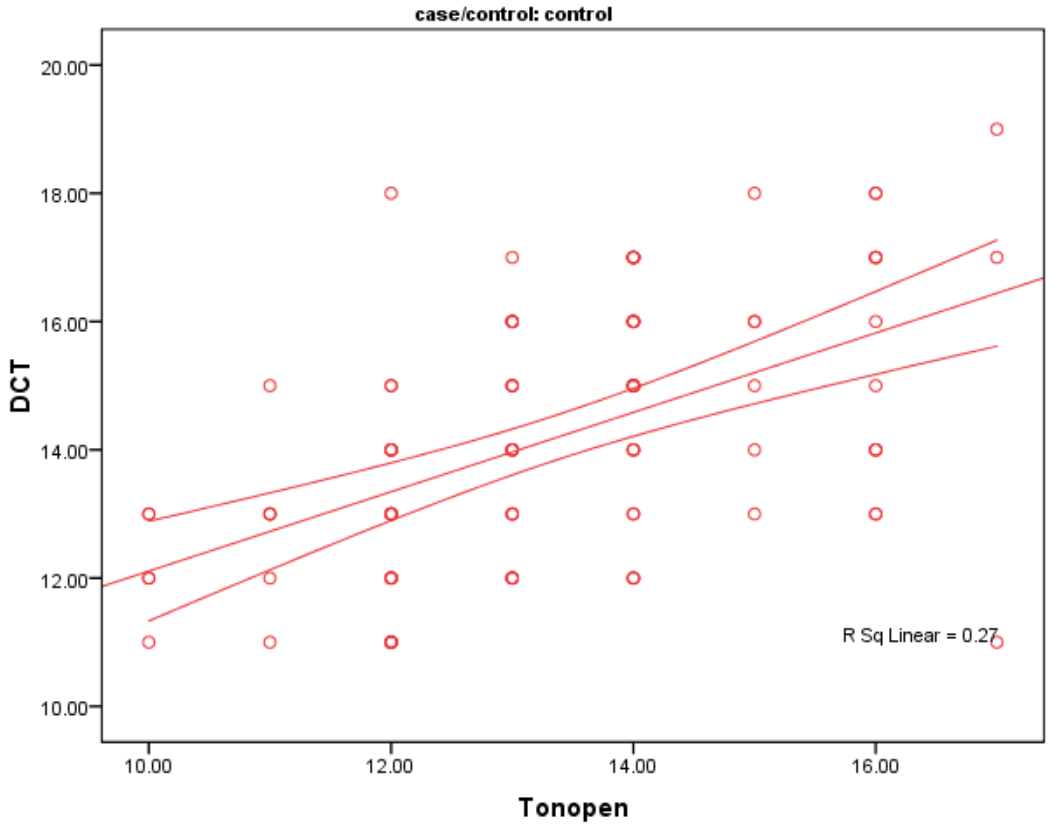
Figure 14 shows the correlation analysis of IOP measurements when taken with DCT and Tonopen in controls. The correlation was significant ($r^2 = 0.27$, $P < 0.001$).

Figure 14 Scatter plot of DCT and Tonopen along with Best Fit line and its 95% CI



In the regression analysis between DCT and Tonopen in controls, it was shown that as IOP measured with Tonopen increased by 1mmHg there was an increase in 0.61mmHg with the DCT ($p < 0.001$). The DCT and Tonopen IOP measurements correlated well in controls.

Correlation of IOP with Central Corneal Thickness (CCT)

The CCT among keratoconus and controls is given in Table 10

Table 10 Mean CCT in cases and controls

Parameters	Keratoconus	Controls
Mean CCT (μ) ± SD	457.16 ± 4.68	520.37 ± 2.89
Range	325 -552	440-577

The mean CCT in the keratoconus group was 457.16 μ and in the control group was 520.37 μ

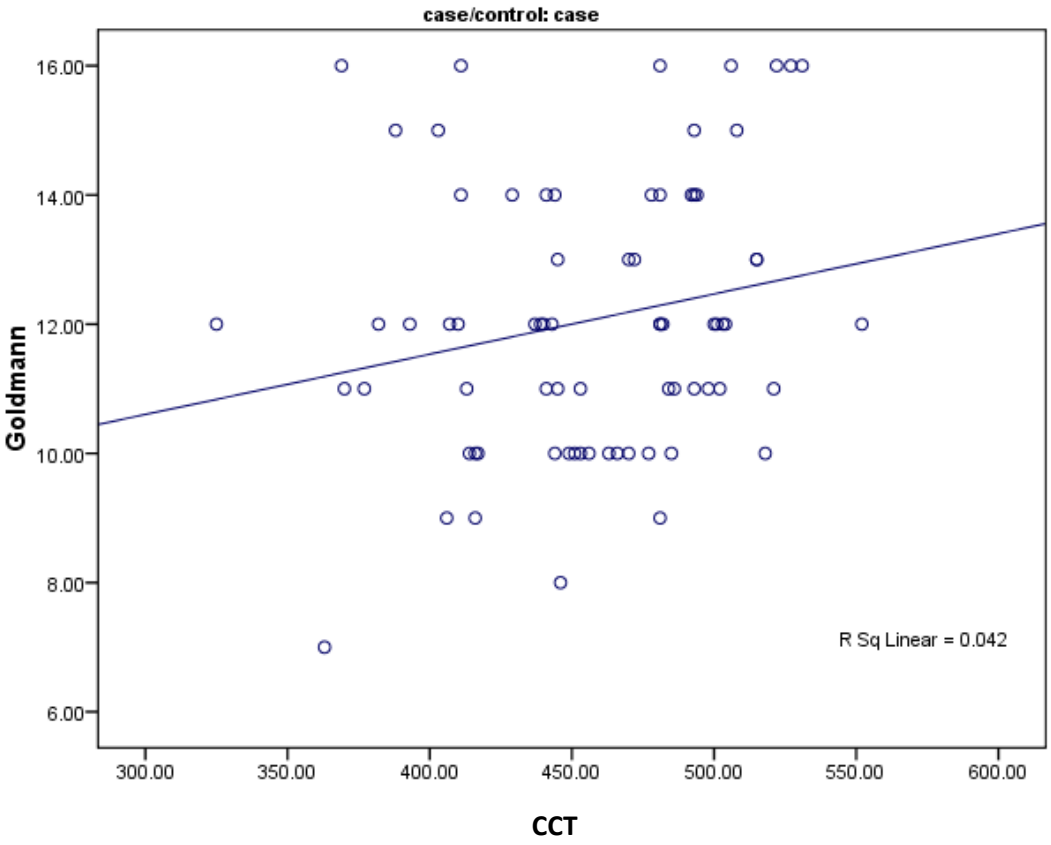
Table 11 Mean CCT and IOP in cases and controls

Group	Mean CCT (μ)	Mean IOP GAT (mmHg)	Mean IOP DCT (mmHg)	Mean IOP Tonopen (mmHg)
Cases	457.16 ± 4.68 (325 -552)	12.068 ± 2.12 (8-16)	14.83 ± 2.49 (10-21)	12.342 ± 1.88 (8-17)
Controls	520.37±2.89 (440-577)	13.94 ±1.96/ (10-19)	14.22±2.0 (11 -19)	13.36±1.70 (10-17)

IOP measured with DCT was noted to be higher than with GAT and Tonopen in the keratoconus group, but in the control group, DCT values obtained were similar to that obtained by GAT but slightly more than that obtained with Tonopen .

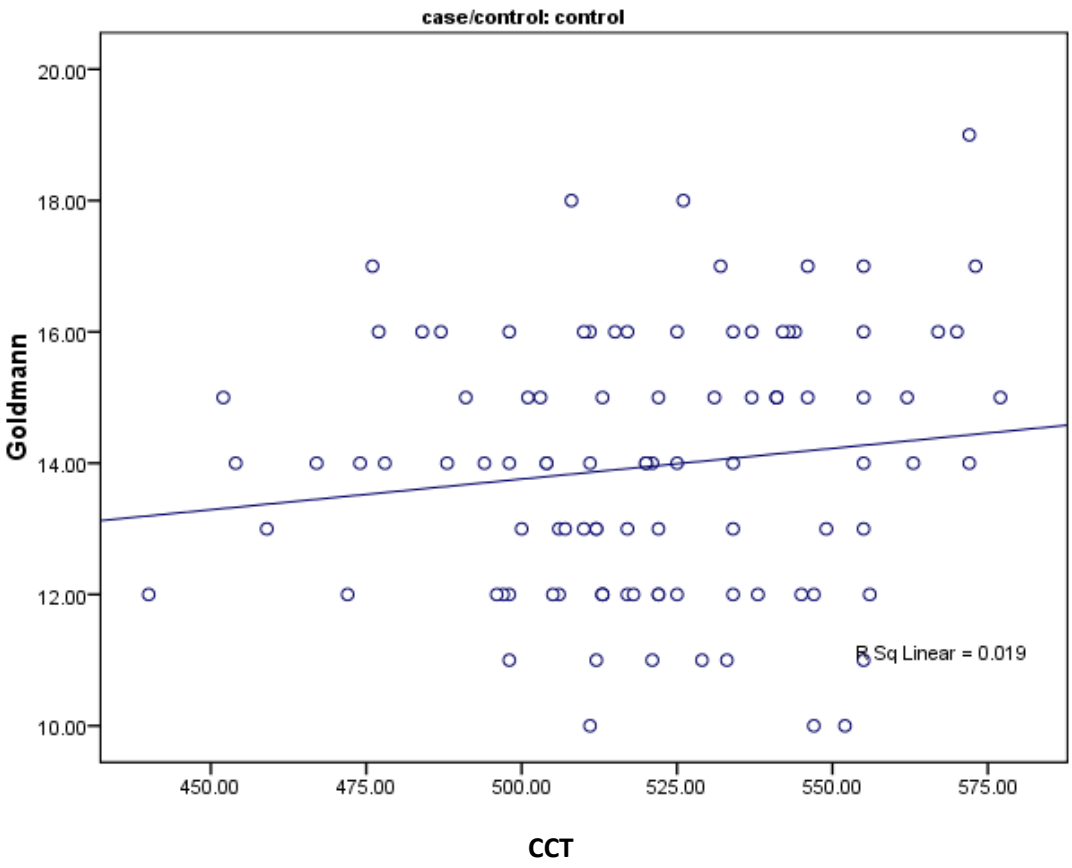
The co relation between GAT IOP and CCT in the keratoconus and control group is shown in Figure 15 and 16

Figure 15 Scatter plot of GAT IOP against CCT in keratoconus along with best fit line



The correlation coefficient of GAT IOP and CCT in the keratoconus group was found to be 0.20 and this was not statistically significant (P = 0.091)

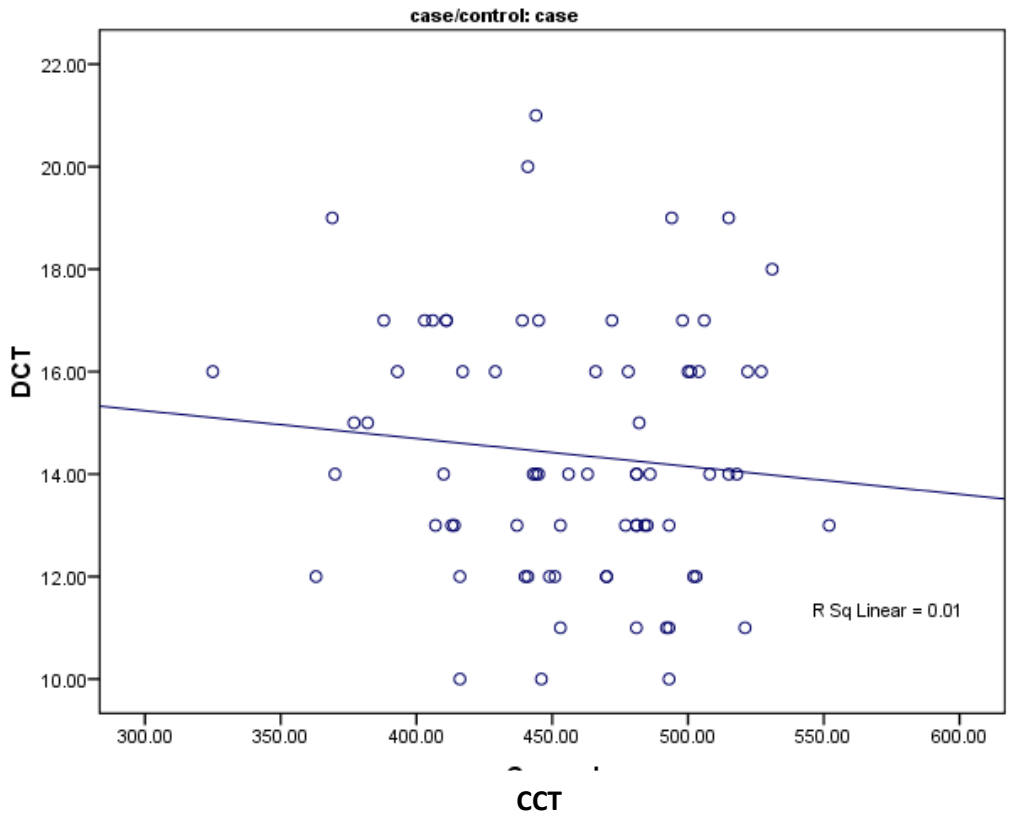
Figure 16 Scatter plot of GAT IOP against CCT in the controls along with best fit line.



The correlation coefficient of GAT IOP and CCT in the control group was found to be 0.13 and this was not statistically significant (P = 0.195).

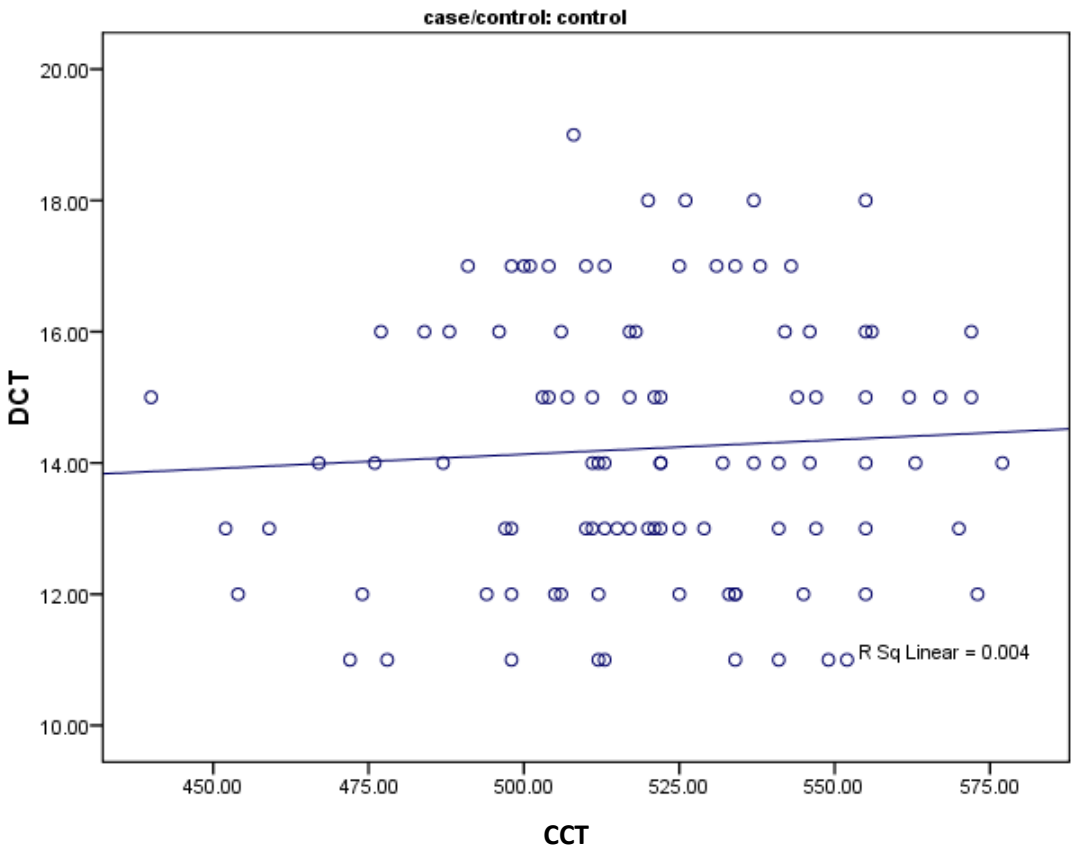
The co relation between DCT IOP and CCT in the keratoconus and control group is shown in Figure 17 and 18

Figure 17 Scatter plot of DCT IOP against CCT in keratoconus along with best fit line



The correlation coefficient of DCT and CCT in keratoconus group was found to be 0.10 and this was not statistically significant (P = 0.451).

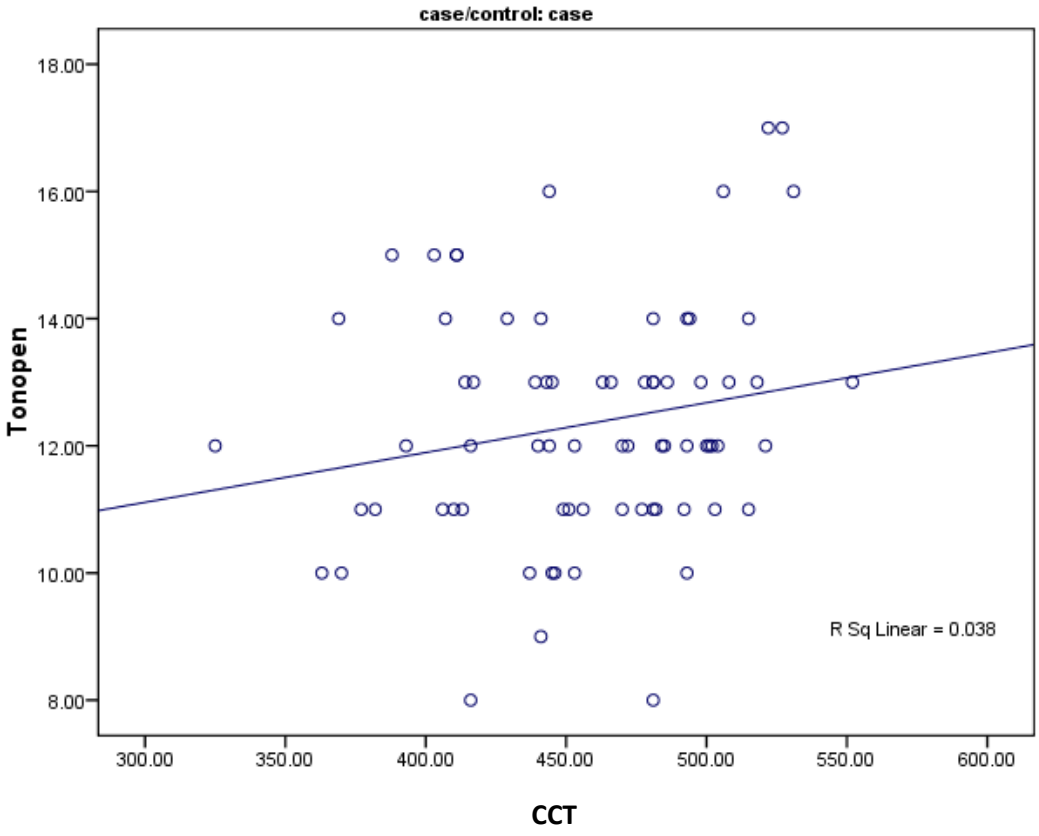
Figure 18 Scatter plot of DCT IOP against CCT in controls along with best fit line



The correlation coefficient of DCT and CCT in controls was found to be 0.04 and this was not statistically significant (P = 0.661).

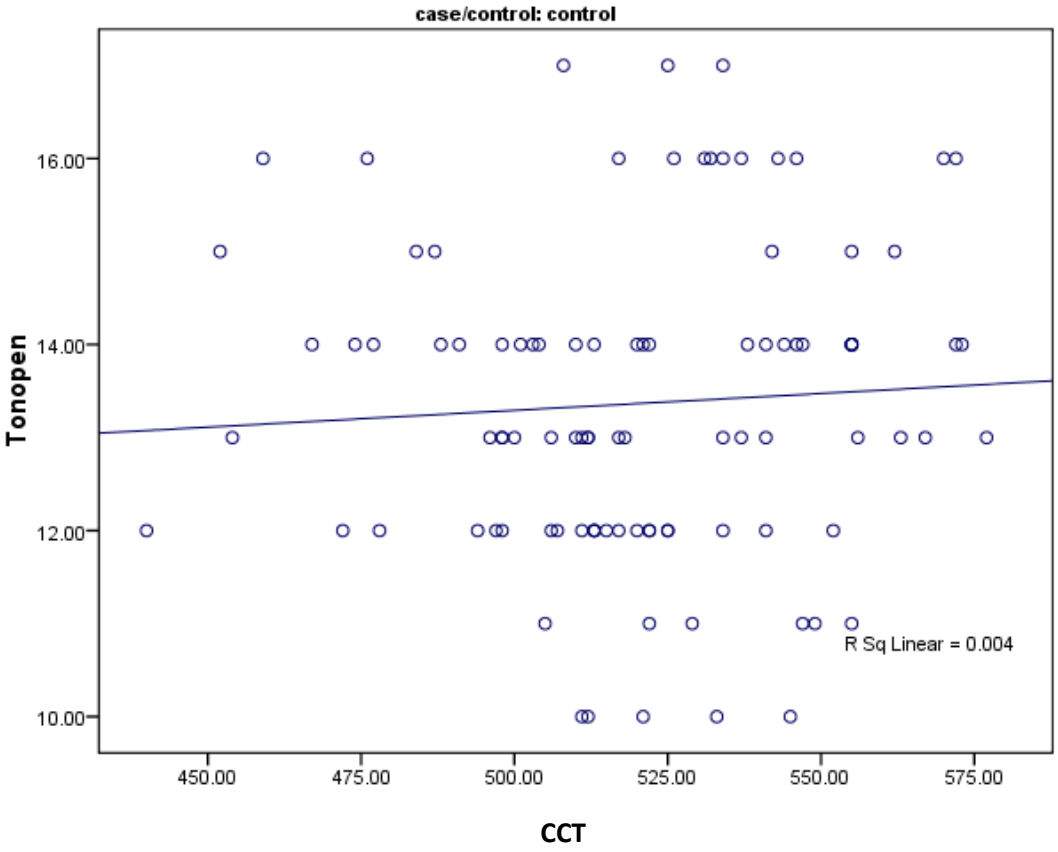
The co relation between Tonopen IOP and CCT in the keratoconus and control group are shown in figures 19 and 20

Figure 19 Scatter plot of Tonopen IOP against CCT in keratoconus



The correlation coefficient of Tonopen IOP and CCT in the keratoconus group was found to be 0.17 and this was not statistically significant (P = 0.135).

Figure 20 Scatter plot of Tonopen IOP against CCT in controls



The correlation coefficient of Tonopen and CCT in the control group was found to be 0.09 and this was not statistically significant (P = 0.369)

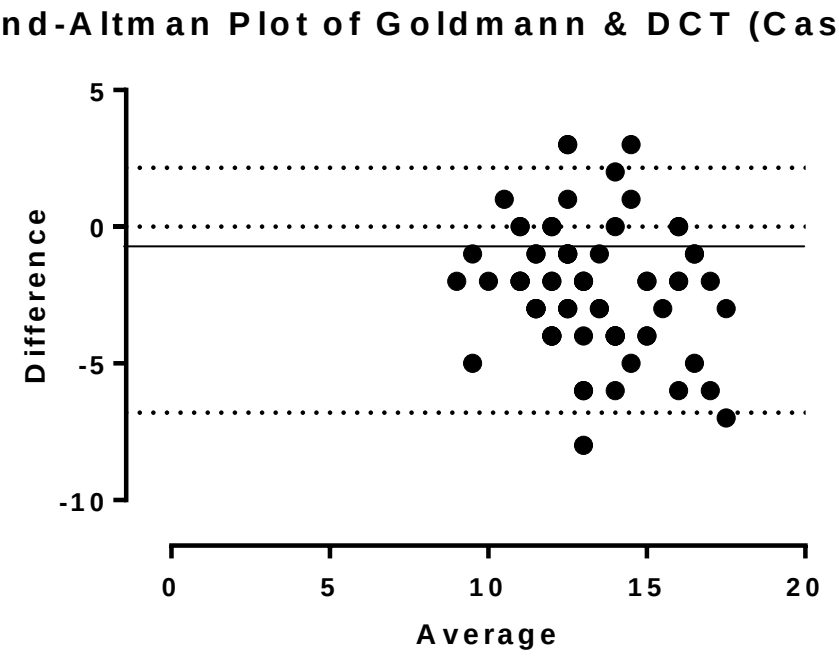
There was poor correlation of DCT and Tonopen IOP with CCT in both groups but a near significance with GAT IOP was seen in both group (cases and controls)

Bland Altman Analysis of agreement between GAT, DCT and Tonopen

Table 12 Bland Altman Analysis of agreement between GAT, DCT and Tonopen IOP in keratoconus

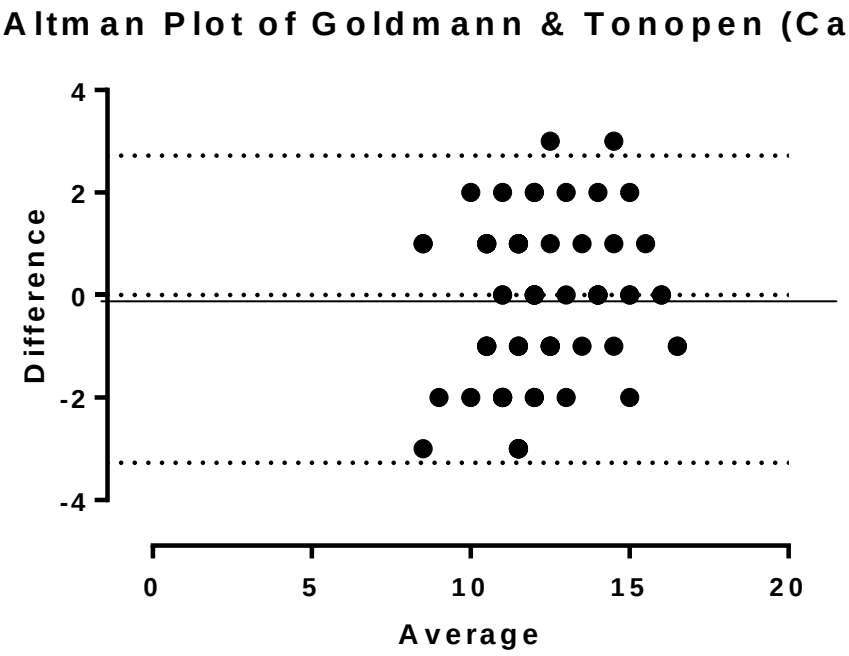
Tonometer	Men difference ± SD (mmHg)	95% Limits of Agreement(mmHg)
GAT – DCT	-2.31 ± 2.28	-6.79 to 2.16
GAT – Tonopen	-0.27 ± 1.52	-3.27 to 2.75
DCT – Tonopen	2.04 ± 1.88	-1.64 to 5.72

Figure 21 Bland – Altman plot showing agreement between GAT and DCT IOP



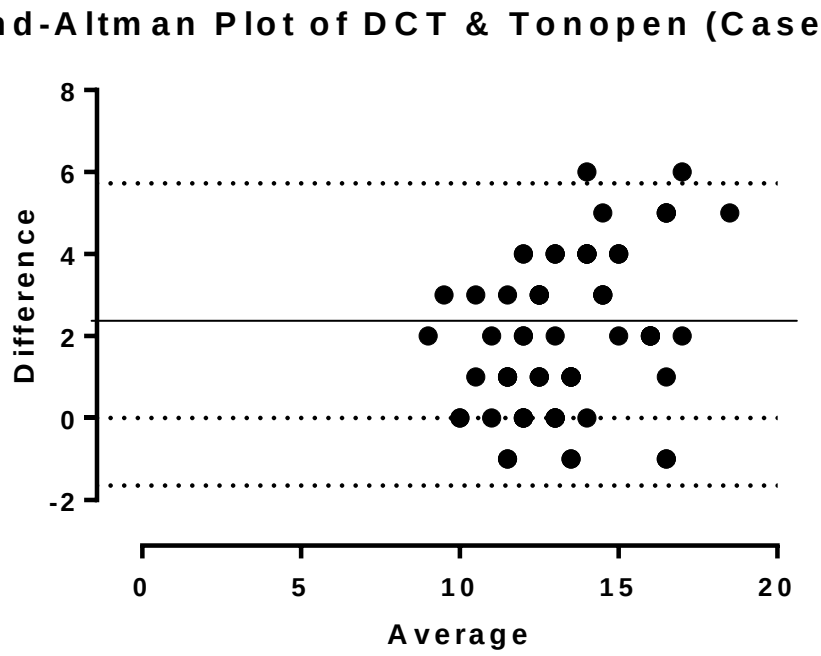
The mean difference between GAT IOP and DCT IOP was -2.32 ± 2.28 (-6.79 to 2.16).. A systematic error of -2.31 was revealed. For greater values of GAT IOP, the DCT showed a positive value.

Figure 22 Bland – Altman plot showing agreement between GAT and Tonopen IOP



The mean difference between GAT IOP and Tonopen IOP was -0.27 ± 1.52 (--3.27 to 2.75). A systematic error of -0.27 was revealed. For higher values of GAT IOP, a greater value of Tonopen IOP was seen

Figure 23 Bland – Altman plot showing agreement between DCT and Tonopen IOP

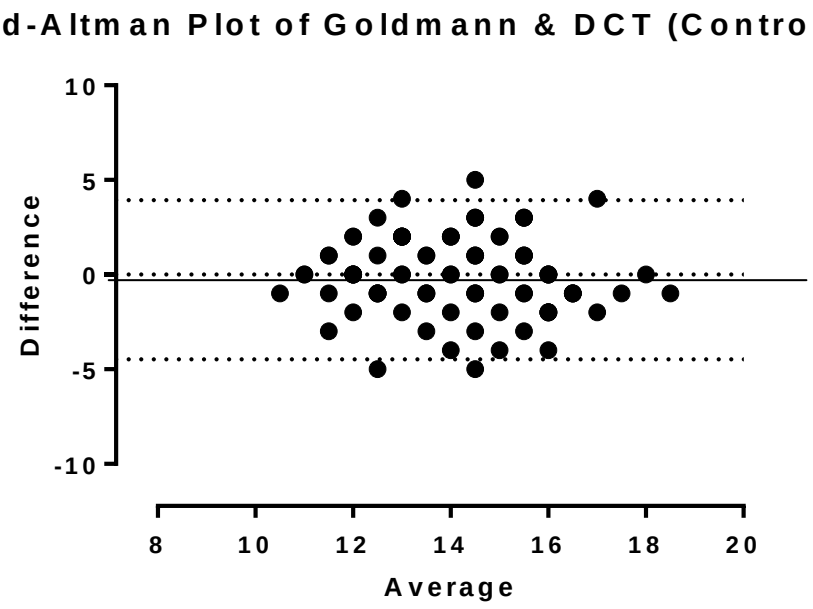


The mean difference between DCT IOP and Tonopen IOP was 2.04 ± 1.88 (-1.64 to 5.72). A systematic error of 2.04 was revealed. IOP DCT values were greater than tonopen IOP values.

Table 13 Bland Altmann Analysis of agreement between GAT, DCT and Tonopen in controls

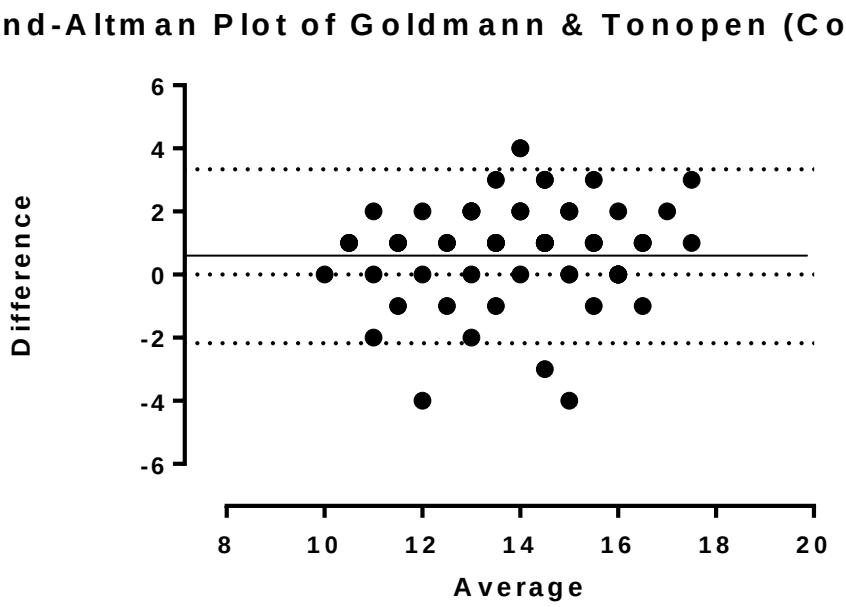
Tonometer	Men difference ± SD (mmHg)	95% Limits of Agreement (mmHg)
GAT - DCT	-0.27 ± 2.14	-4.48 to 3.93
GAT - Tonopen	0.58 ± 1.40	-2.17 to 3.33
DCT - Tonopen	0.82 ± 1.8	-2.81 to 4.64

Figure 24 Bland – Altman plot showing agreement between GAT and DCT IOP



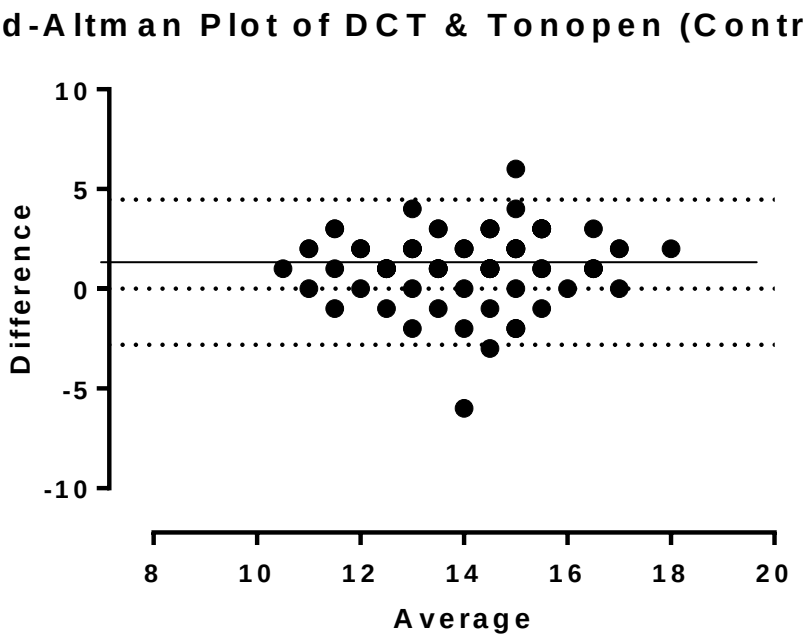
The mean difference between GAT IOP and DCT IOP was -0.27 ± 2.14 (-4.48 to 3.93). A systematic error of -0.27 was revealed. DCT IOP did not show any variation in both low and high IOPs of GAT.

Figure 25 Bland – Altman plot showing agreement between GAT and Tonopen IOP



The mean difference between GAT IOP and Tonopen IOP was 0.58 ± 1.40 (-2.17 to 3.33) A systematic error of 0.58 was found. IOP as obtained by Tonopen did not show any particular variation at ranges of GAT IOP.

Figure 26 Bland – Altman plot showing agreement between DCT and Tonopen IOP



The mean difference between DCT IOP and Tonopen IOP was 0.82 ± 1.8 (-2.81 to 4.64). A systematic error of 0.82 was found. DCT IOP was higher than Tonopen IOP in both low and high ranges of Tonopen IOP.

Reproducability of IOP

We analysed the reproducibility of the IOP's after one hour with all three tonometers in keratoconus and controls and as given in table 14 The reproducibility was evaluated using Spearman's correlation coefficient

Table 14 Reproducibility of IOP (ρ = Spearman's correlation coefficient)

IOP	ρ (cases)	ρ (controls)	p value
GAT – GAT_{1hour}	0.97	0.90	<0.001
DCT – DCT_{1hour}	0.93	0.90	<0.001
Tonopen – Tonopen $_{1\ hour}$	0.94	0.91	<0.001

Excellent correlation was noted in both groups using GAT, DCT and Tonopen.

DISCUSSION

Discussion

A major factor in the diagnosis and management of glaucoma is the accurate determination of the intraocular pressure. Due to the corneal changes in keratoconus, exact IOP measurements have been a challenge. The Goldmann applanation tonometer fifty years after its development still remains the gold standard for measuring the intraocular pressures. It is currently the most accepted tonometer around the world; however many previous studies have shown errors with the GAT in structurally altered corneas. These errors led to a search of a new tonometer which can measure IOP independently of the corneal parameters. The recently developed Pascal tonometer uses contour matching instead of applanation to measure IOP. Several studies with this dynamic contour tonometer in patients with keratoconus have demonstrated that IOP readings are not affected by corneal parameters.(28) Conversely, other studies have suggested that corneal changes do affect IOP readings with the dynamic contour tonometer.(15,16,55) The hand held Tono-Pen is widely available and is based on the Mackay-Marg principle. It is easy to use, portable, and produces results similar to the Mackay-Marg tonometer in the presence of corneal surface irregularities.(96). Since the results of the Ocular Hypertensive Treatment study have been published, it is known that CCT is as an important factor because of its influence on the IOP measurement.(97)

Recent discoveries have led to the development of new tonometers, to obtain an IOP reading independent of corneal factors. Studies with tonometers like the ORA which measures other corneal biomechanical properties like corneal hysteresis and rigidity have looked into the possible influence of these factors on IOP recordings and their possible prognostification in glaucoma. A final goal has been to provide a tonometer that is easy to use, reliable and accurate and can be used by patients at home.(98)

Glaucoma and ocular hypertension may co-exist in keratoconus patients. Hence a reliable IOP measurement is to be made in these patients to assist in the diagnosis and monitoring of treatment. New tonometers such as the DCT and ORA have been developed to overcome the problems associated with GAT. Numerous studies have been done on keratoconic corneas using different tonometers, however there were no studies done in Indian eyes.

The onset of keratoconus occurs at about the age of puberty. The cornea begins to thin and protrude, causing irregular steepening of the corneal curvature and resulting in irregular astigmatism. Typically the process continues for a period of 10 to 20 years until the progression gradually stops due to stiffening of the cornea with age as a result of ultrastructural changes in the collagen fibrils of the corneal stroma.(99,100)

The mean age of patients with keratoconus in our study was 22.3 ± 8.1 years. with a range of 10-52 years. This is similar to the Sao Paulo study where the mean age was 22 ± 6.8 years.(16) In the study done by Meyenberg et al(15), the mean age was 47.8 ± 19.0 years, 45.3 ± 12.5 (28 -72) years in the study done by Ozbek.(47) Various other studies have reported a mean age of around 30 years.(9,14,28,101) We recruited patients lesser than 40 years since keratoconus is a disease seen in younger age group.

Keratoconus does not show any particular gender predilection. Females (56%) were more in number compared to males (44%) in our study. In the study by Scott et al there were equal number of males (50%) and females (50%) whereas in other studies by Ozbek et al(58% males and 42% females), Papastergiou et al (56% males and 44% females) males predominated in numbers.

When we looked at the distribution of refractive errors among controls majority 65% were emmetropes. Astigmatism was present in 21% of our patients. However we excluded

patients with more than two dioptres of atigmatism as astigmatism of 3 diopters can cause a rise of 1mmHg(102) change in the IOP and because they could be forme fruste keratoconus.

Keratoconus may occur in one eye initially but commonly affects both eyes with one eye being more severely affected than the other.(37) We found that 78% of our patients had bilateral keratoconus. Clinical signs of keratoconus vary depending on the severity of disease. 54 of the 73 keratoconic eyes in our study had Vogt's striae which indicate they had moderate to advanced disease. The mean flat keratometry among our keratoconic patients were in the range of 43.47 to 67.40 D again indicates that some of them had severe keratoconus.

The mean CCT in the in the keratoconus group was 457.16 ± 4.68µ (range 325 -552µ) whereas among controls it was 520.37 ± 2.89 µ (range 440-577µ This is similar to the study by Mollan et al where the mean CCT was found to be 453.0µ with a range of 342- 543µ (n=76) (ref Mollan et al). Others like Barreto et al (n=49) showed mean CCTs of 387.8 ± 53.3 µm (range, 298-468 µm) in keratoconus and 551 ± 15.3 µm (range, 530-576 µm) in controls, Meyenberg et al have reported CCT as 454 ± 60.3 µm (n =59) and 462 ± 62 µm Papastergiou et al (n=46).

The mean IOP among keratoconus patients was similar with GAT and Tonopen (12.06 ± 2.12 and 12.34 ± 1.88 mm Hg respectively). However IOP measured by DCT was higher (14.83 ± 2.49 mm Hg). The mean IOP measured in the control group was 13.94 ± 1.96 mm Hg with GAT, 14.22 ± 2.04 mm Hg with DCT and 13.36 ± 1.70 mm Hg with Tonopen (table 6). When the IOP distribution with the 3 tonometers among keratoconus and controls were compared using the box and whisker plot as in figures 6,7 and 8 it was noted that the GAT and Tonopen IOP values were higher in the controls but the DCT IOP values were similar in cases as well as controls

The box and whisker plot of IOP distribution shows the mean and range of IOP as obtained by the various tonometers. Figures 4 and 5 show the mean and range of IOP as obtained by the various tonometers among keratoconus and controls. Note that the DCT values obtained in keratoconus were significantly higher than those of GAT and Tonopen. In keratoconus the 50th percentile was 14mm Hg for DCT and it was 12mm Hg for GAT and Tonopen. The DCT values obtained in the control group were similar to those obtained by GAT but slightly more than those obtained with Tonopen

Studies in normals have shown that CCT does not significantly affect the IOP recordings with DCT.(13,47) This is consistent with our results in which the DCT IOP in normals (with average CCT 520μ) showed similar values as by GAT (table 6 and figure 5). However in patients with keratoconus who have thinner corneas (average CCT 457μ), the DCT values were higher than those obtained by GAT (table 5 & figure 4). The artifactual appearance of lower IOP measured in Keratoconus is probably due to low mean CCT in keratoconus, so if a correction factor is added then IOP will be same as controls. Hence DCT values are likely to be more representative of the true IOP compared to GAT unless the GAT measured IOP is corrected for the reduced corneal thickness. Other authors(16,49,55) have reported higher IOP recordings by DCT as compared to GAT in patients with keratoconus similar to our findings. Barreto et al obtained mean IOP's of 10.3 ± 1.8 mm Hg in keratoconus and 14.3 ± 0.75 mm Hg in normal patients. With the DCT the mean measurement was 14.6 ± 2.09 mm Hg in keratoconus and 17.4 ± 3.1 mm Hg in normals. Bayer et al obtained mean IOPs of 10.96 ± 2.8mmHg with GAT and 15.42±2.7mmHg with the DCT

In our study population the tonopen IOP was similar to the GAT IOP in the keratoconus group (Table 6). The CCT in this group was 457.16 ± 4.68μ (range 325 -552μ). Similar findings have been reported in a study by Browning et el where IOP was studied in 37 eyes with keratoconus. They reported IOP measurements of 10.9 +/- 2.7 mmHg with Tonopen and

10.5 +/- 2.2 mmHg with GAT. The CCT was 455+/- 67 microns in this group. However Mollan et al in a study of 76 keratoconus eyes found that higher IOP recordings were obtained by DCT, ORA and Tonopen as compared to GAT. The CCT in the study group was 453.0 (SD 55.8, range 342- 543 microns). They also reported that apart from DCT, all the other techniques tended to measure higher IOPs in thicker corneas. Hence there are varying reports of Tonopen IOP being similar to or higher than GAT IOP in patients with keratoconus.

Though studies comparing GAT and Tonopen have shown that they have good correlation in normal range of IOP and poor correlation in high and low range of IOP. (10,103) there is paucity of data regarding correlation of Tonopen IOPs vs GAT in very thin corneas as in keratoconus. Bhan et al(58) studied in normal eyes , the effect of corneal thickness on intraocular pressure measurement as measured by GAT, pneumotonometry and tonopen and found that Tonopen was least affected by CCT. However the mean CCT in their study was higher (551.53+/- 0.49 microns).

Tonopen being an applanation tonometer with lesser area of contact than GAT, one would expect the measurements to be affected by a lesser magnitude by CCT than GAT. This may explain the slightly higher IOPs recorded by Tonopen in keratoconic eyes as compared to GAT IOP as reported by Mollan et al. However in our study we found that Tonopen IOP was near equal to GAT IOP in keratoconus. There seems to be no consistent pattern of how CCT affects Tonopen IOP recordings. There is not enough evidence regarding Tonopen IOP of data regarding tonopen IOP and its relation with thin CCT or other unknown corneal structural factors peculiar to keratoconus and its particular stages/severity which could result in varying IOP measurements in patients with varying stages of the disease. This could be the reason for the varying results of IOP recordings with Tonopen reported in different studies. A study looking into measurement of Tonopen IOP in keratoconus patients subgrouping the

eyes based on CCT, severity of the keratoconus as well as structural variations would proabaly yield better understanding of the results of variable IOP recordings reported in keratoconus with tonopen and other methods of IOP measurements.

Agreement of tonometers

Based on Statistical Methods of rates and Proportions by Joseph L Fleiss greater than 0.75 was taken to represent excellent agreement beyond chance, values below 0.40 was taken to represent poor agreement beyond chance, and values between 0.40 and 0.75 was taken as fair to good agreement beyond chance as the agreement cut offs in the present study.

Looking into the agreement between the three tonometers, we found moderate degree of agreement between DCT and GAT measurements among both cases (keratoconus) and controls (normals) with ICC of 0.62 and 0.64 respectively. Excellent agreement was found between Tonopen and GAT among both cases and controls with ICC of 0.83 and 0.81 respectively. However the agreement was fair between DCT and Tonopen IOP recordings among both cases and controls with ICC of 0.51 and 0.59 respectively. Bland Altmann analysis (figure 21 – 26) showed similar agreement as above among the cases and controls with the different methods of IOP measurement. Also DCT showed consistently higher IOP than GAT among cases with a Systematic error of -2.31 (figure 21). Firat et al (n =102) reported similar findings in keratoconus eyes using GAT and DCT, along with other studies.(9,14–16,47) Bayer et al (n=120) reported poor agreement between DCT and GAT.(55) Univariate regression analysis showed good correlation between the three tonometers in both cases and controls (figure 9 -14).

In our study there was poor correlation between CCT and IOP recordings measured by all three tonometers as shown in figure (15-20).

Similar to our study, other studies also have reported poor co-relation of IOP as measured by different methods of tonometry and CCT. Ozbek et al studied 53 eyes which included keratoconus (n=29), penetrating keratoplasty (n=21) and pellucid marginal degeneration (n= 3). They found a positive co-relation between CCT and both GAT and Tonopen measurements but was not statistically significant. Schadle et al (n=93) did not find any correlation between GAT and DCT with the CCT in keratoconus ($p > 0.05$). Pache et al (n =100) in normals and Viestenz et al (n=92) among keratoplasty eyes did not show any correlation with GAT and CCT. Mollan et al (n= 76) in keratoconus eyes compared IOP recordings by GAT, ORA, DCT and Tonopen. They found that corneal factors like corneal hysteresis and cornea resistance factor may be of more importance than CCT in causing inaccuracies in applanation tonometry techniques.

Studies(14–16) have shown that IOP measurements in irregular corneas by DCT is less dependent on CCT as compared to GAT. Studies looking into the effect of CCT on Tonopen IOP recordings have shown varying results.(10) Most studies in keratoconus patients have found DCT to be least affected by CCT compared to other methods of tonometry. (16,47,104)

We found a good reproducibility of all three techniques in keratoconus as well as controls. Our study found that the IOP recordings had good repeatability when IOP measurement was repeated after one hour and analysed using Spearman's correlation coefficient. Only few studies have been reported which has looked into reproducibility. We did not find any report of studies looking into reproducibility of IOP measurements in keratoconus using different tonometers. We looked at reproducibility in one hour rather than later during the day in order to avoid possible bias which could occur due to diurnal variation in IOP. However the reproducibility of the IOP measurements with various tonometers has previously been reported in normals. Medline showed no results in keratoconic eyes.

Summary

We conclude that DCT IOP and corrected GAT IOP were suitable methods for IOP measurement of keratoconus patients. There are concurrent reports of variability of tonopen recordings in various studies. Tonopen recordings showed a fair degree of agreement with DCT/tonopen. GAT has a diameter 0f 3.06 mm and DCT having a slightly more diameter of 7.5 mm tmay not be adequate in keratoconic corneas as the diameter exceeds that of the cone, hence a ideal tonometer would be the one with a lesser surface area which could indent only the small region of the cornea. The tonopen has a small surface area of applanation but however due to varying reports in literature regarding the inconsistency of measuring the IOP it may not be ideal. Newer tonometers like the ORA which takes into account the biomechanical properties of the cornea such as the corneal hysteresis may be show a promising role in determining a correct IOP in patients with keratoconus, however there is limited data regarding its reliability and agreement in keratoconus. We found a good reproducibility of all three techniques of IOP measurement in keratoconus as well as controls.

LIMITATIONS OF THE STUDY

Limitations of the study

1. Effect of corneal curvature and axial length were not analysed in the study

2. Other corneal biomechanical properties like corneal hysteresis, were not analysed. This was not defined in the scope of our study.

3. We could not look into factors such as CRF as we were not equipped with the instruments in our department.

CONCLUSIONS

Conclusions

1. All three methods of IOP measurement with DCT, GAT and Tonopen showed fair to good correlation. There was excellent agreement between GAT and Tonopen.

2. DCT IOP measurements were higher than GAT measurements.

3. There was no correlation of GAT, DCT and Tonopen with the CCT.

4. IOP measurements with all three instruments were found to be reproducible in keratoconus as well as normals.

5. Intraocular pressure measured with DCT and CCT corrected IOP measured with GAT are recommended as suitable methods for IOP measurement for keratoconus patients. It is also important to choose an instrument which is best suited for a particular patient and should be consistently used for the long term follow up.

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ANNEXURE

ANNEXURE I

IRB APPROVAL FORM

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr. B J Prashantham, M.A, M. A., Dr. Min (Clinical)
Director, Christian Counselling Centre
Chairperson, Ethics Committee

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas
MD,MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

August 26, 2013

Dr. Shishir Verghese
PG Registrar
Department of Ophthalmology
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
To compare the degree of agreement of intraocular pressure in patients with keratoconus using Goldmann Applanation Tonometry (GAT), Dynamic Contour Tonometry (DCT) and Tonopen.
Dr. Shishir Verghese, Junior Resident, Ophthalmology, Dr. Pushpa Jacob, Dr. Arathi Simha R, Ophthalmology.

Ref: IRB Min. No. 8337 [OTHER] dated 18.06.2013

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Pushpa Jacob, Department of Ophthalmology, CMC

TEL : 0416 - 2284204, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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August 26, 2013

Dr. Shishir Verghese
PG Registrar
Department of Ophthalmology
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
To compare the degree of agreement of intraocular pressure in patients with keratoconus using Goldmann Applanation Tonometry (GAT), Dynamic Contour Tonometry (DCT) and Tonopen.
Dr. Shishir Verghese, Junior Resident, Ophthalmology, Dr. Pushpa Jacob, Dr. Arathi Simha R, Ophthalmology.

Ref: IRB Min. No. 8337 [OTHER] dated 18.06.2013

Dear Dr. Shishir Verghese,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "To compare the degree of agreement of intraocular pressure in patients with keratoconus using Goldmann Applanation Tonometry (GAT), Dynamic Contour Tonometry (DCT) and Tonopen." on June 18, 2013.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Informed Consent Form and Information Sheet (English and Tamil)
3. Cvs of Drs. ShishirVerghese, Pushpa Jacob, ArathiSimha R
4. A CD containing documents 1 - 3

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on June 18, 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

ANNEXURE I

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VELLORE 632 002, INDIA

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Dr. Nihal Thomas
MD,MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
Dr. Anil Kuruvilla	MBBS, MD, DCH	Professor, Neonatology, CMC.	Internal, Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Chandrasingh	MS, MCH, DMB	Urology, CMC	Internal, Clinician
Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo), FRACP	Professor, Endocrinology, CMC	Internal, Clinician
Dr. Anuradha Bose	MBBS, DCH, MD, MRCP, FRCPCH	Professor, Pediatrics, CMC	Internal, Clinician
Dr. Anup Ramachandran	PhD	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal, Basic Medical Scientist
Dr. Binu Susan Mathew	MBBS, MD	Associate Professor, Dept. of Clinical Pharmacology	Internal, Pharmacologist
Dr. Ellen Ebenezer Benjamin	M.Sc	Maternity Nursing, CMC	Internal, Nurse
Dr. Rajesh Kannangai	MD, PhD.	Professor & In-charge Retrovirus Laboratory (NRL under NACO), Clinical Virology, CMC	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS M Ch	Professor, Neurological Sciences, CMC	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC	Internal, Clinician
Dr. Ashok Chacko	MD, DM, FRCP, FRCPG, FIMSA, FAMS	Director, Institute of Gastroenterology and Liver Disease, Madras Medical Mission, Chennai	External, Clinician

3 of 5

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ANNEXURE I

IRB APPROVAL FORM

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VELLORE 632 002, INDIA

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MD,MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Bobby John	MBBS, MD, DM, PHD, MAMS	Cardiology, CMC	Internal, Clinician
Mrs. Pattabiraman	B Sc, DSSA	Social Worker, Vellore	External, Lay Person
Mr. Sampath	B Sc, BL	Advocate	External, Legal Expert
Mr. Joseph Devaraj	B Sc, BD	Chaplain, CMC	Internal, Social Scientist
Dr. B. J. Prashantham (Chairperson), IRB Blue - Internal	MA (Counseling), MA (Theology), Dr Min(Clinica	Chairperson(IRB)& Director, Christian Counselling Centre, Vellore	External, Social Scientist
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL	Sr. Legal Advisor, CMC.	Internal, Legal Expert
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

4 of 5

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ANNEXURE I

IRB APROVAL FORM

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr. B J Prashantham, M.A, M. A., Dr. Min (Clinical)
Director, Christian Counselling Centre
Chairperson, Ethics Committee

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas
MD,MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Fluid Grant Allocation:

A sum of Rs. 60,000/- (Rupees Sixty Thousand only) will be granted for 1 year 6 months.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Pushpa Jacob, Department of Ophthalmology, CMC

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

ANNEXURE II

INFORMATION SHEET

Degree of Agreement of Intraocular pressure in patients with a range of corneal thickness using GoldmannApplanation tonometry, Tonopen and Dynamic contour tonometry.

Information sheet

You are being requested to participate in a study to look at the agreement of intraocular pressures in normal patients and patients with Keratoconus. We hope to recruit around 200 participants for this study. Half of the participants will be patients with Keratoconus and other half patients with normal eyes.

We want to compare the three instruments for checking the intraocular pressure in normal patients as well as patients with keratoconus.

If you agree to participate in this study, your intraocular pressure will be measured using the three different instruments for both eyes followed by the central corneal thickness which will be measured by a pachymeter and the values will be noted down and compared.

Prior to this you will undergo refraction and BCVA and you will be subjected to videokeratography, unless you have it done within 3 months.

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

There are no direct benefits, but information gathered from this study will make us understand the correlation in the intraocular pressure between the three instruments their dependence or independence on the corneal thickness and which instrument we will prefer to use in the OPD for checking IOP in thin corneas, especially in patients with keratoconus.

There will be no additional costs involved in the study. The whole procedure will not take more than 20 minutes.

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr.ShishirVerghese (tel: 0416 2281201 / 9952198506) or email: shishirverghese@gmail.com

ANNEXURE III

CONSENT FORM

Informed consent

Degree of Agreement of Intraocular Pressure using GoldmannApplanation Tonometry, Tonopen and Dynamic Contour Tonometry in patients over a range of Corneal Thickness

Study number: **Date:**

Name of participant:

Hospital number:

I confirm that I have been explained that I have been given the option of undergoing testing to check intraocular pressure and central corneal thickness by GoldmannApplanation Tonometer, Tonopen , Dynamic contour tonometry and Pachymeter. I have understood the risks and complications of this study and have had the opportunity to ask the investigators any questions I may have had. I understand that my participation in the study is voluntary and that I can leave the study at any given time, without having my medical care or legal rights being affected. I agree that the investigators and their team have the access to all the data that I may provide them. I accept to share the data obtained during analysis in the faith that it will be used only for scientific purposees. I accept that my identity will not be revealed if the data be published or sent to a third party. I agree not to restrict the scientific use of any of the data or results that may arise from this study.

Understanding all the above, I give my consent for taking part in the above mentioned study.

Patient's/ Legally acceptable representative's signature (or thumb impression) with date

Signature of a witness with date

Signature of the investigator with date

Christian Medical College, Vellore

Department of Ophthalmology

ANNEXURE IV

PATIENT PROFILE

PATIENT PROFILE

NAME: HOSPITAL NUMBER: AGE: DATE OF BIRTH:

NORMAL: Yes/No KERATOCONUS: Yes/No

EYE WITH KERATOCONUS

DIAGNOSIS Right Eye Left Eye

	RE	LE
BCVA		
REFRACTION		

KERATOCONUS SIGNS

EXTERNAL SIGNS	RIGHT EYE	LEFT EYE
Munson's Sign		
Rizzuti's Sign		
Sicssoring Reflex		

SLIT LAMP SIGNS	RIGHT EYE	LEFT EYE
Stromal Thinning		
VogtsStriae		
Fleicher's Ring		
Scarring		

TMS AGREEMENT(Klyce/Madea)

FEATURES	RIGHT EYE	LEFT EYE
Axial Topography		
Flat K >51D		
KPI>0.23		

DSI>2.4		
OSI>2.0		
CSI>1.25		

IOP 1

INSTRUMENTS	RE IOP1 (S)	RE IOP2 (2min)	LE IOP1 (S)	LE IOP2 (2 min)
GOLDMANN APPLANATION				
DCT	QF	QF	QF	QF
TONOPEN WITH 5% Std D				

IOP2 (After one hour)

INSTRUMENTS	RE IOP1 (S)	RE IOP2 (2min)	LE IOP1 (S)	LE IOP2 (2min)
GOLDMANN APPLANATION				
DCT	QF	QF	QF	QF
TONOPEN WITH 5% Std D				

CENTRAL CORNEAL THICKNESS

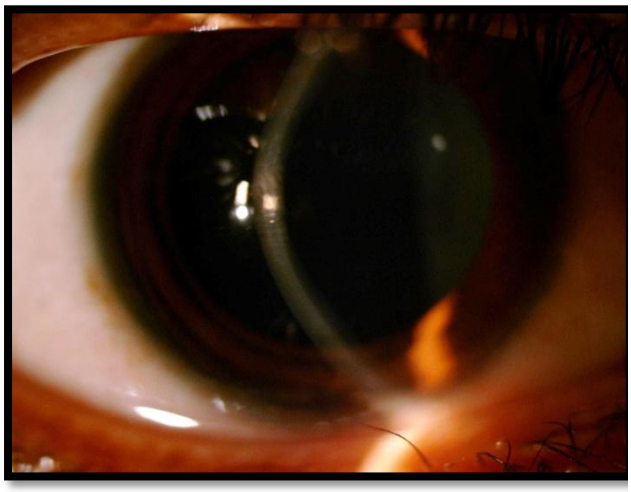
	RIGHT EYE	LEFT EYE
VALUE 1		
VALUE 2		

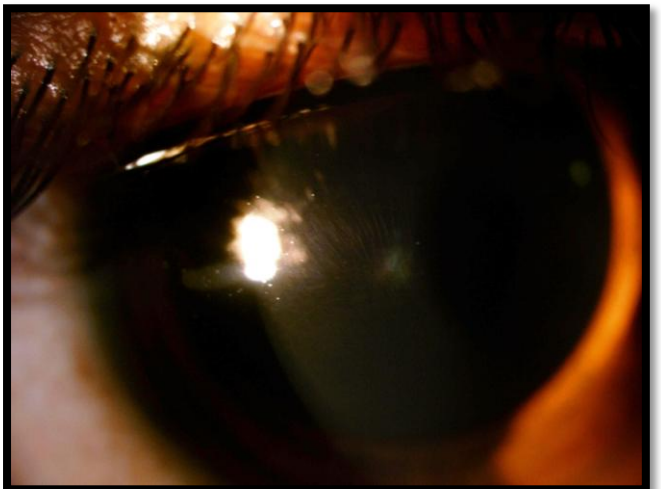
PATIENT INCLUDED AS

- CASE/CONTROL
- IF CASE, PRIMARY EYE STUDIED (RIGHT EYE/LEFT EYE/BOTH EYES)

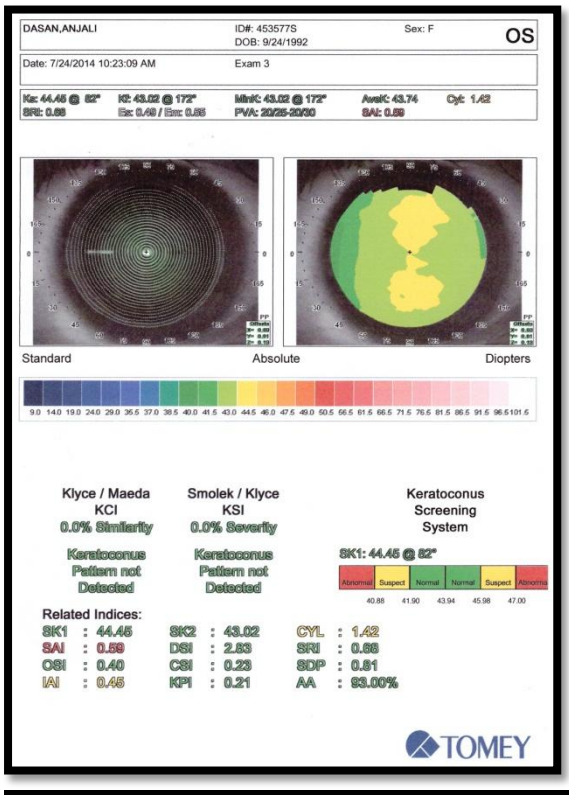
ANNEXURE V

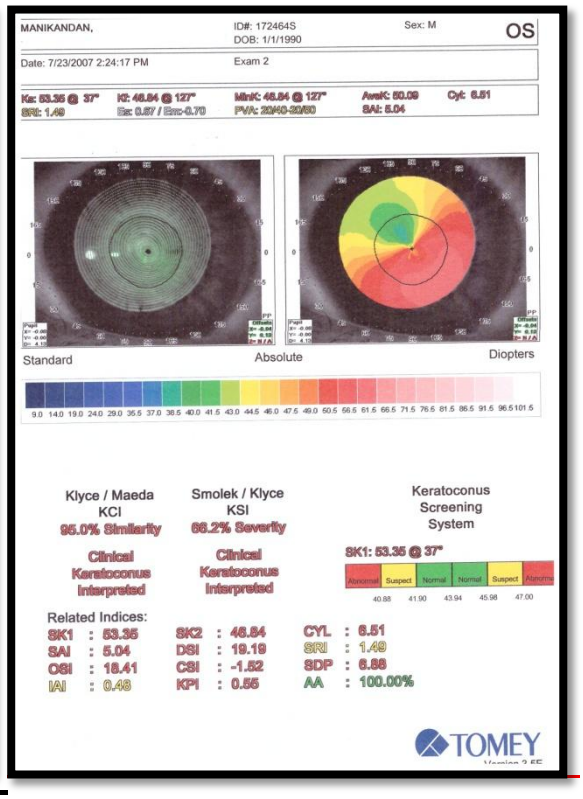
PICTURES





KERATOCONUS WITH CORNEAL PROTRUSION **VOGTS STRIAE**





TOPOGRAPHY OF NORMAL PATIENT TOPOGRAPHY OF KERATOCONUS

TONOMETERS

TONOPEN

GOLDMANN APPLANATION TONOMETER

DYNAMIC CONTOUR TONOMETER

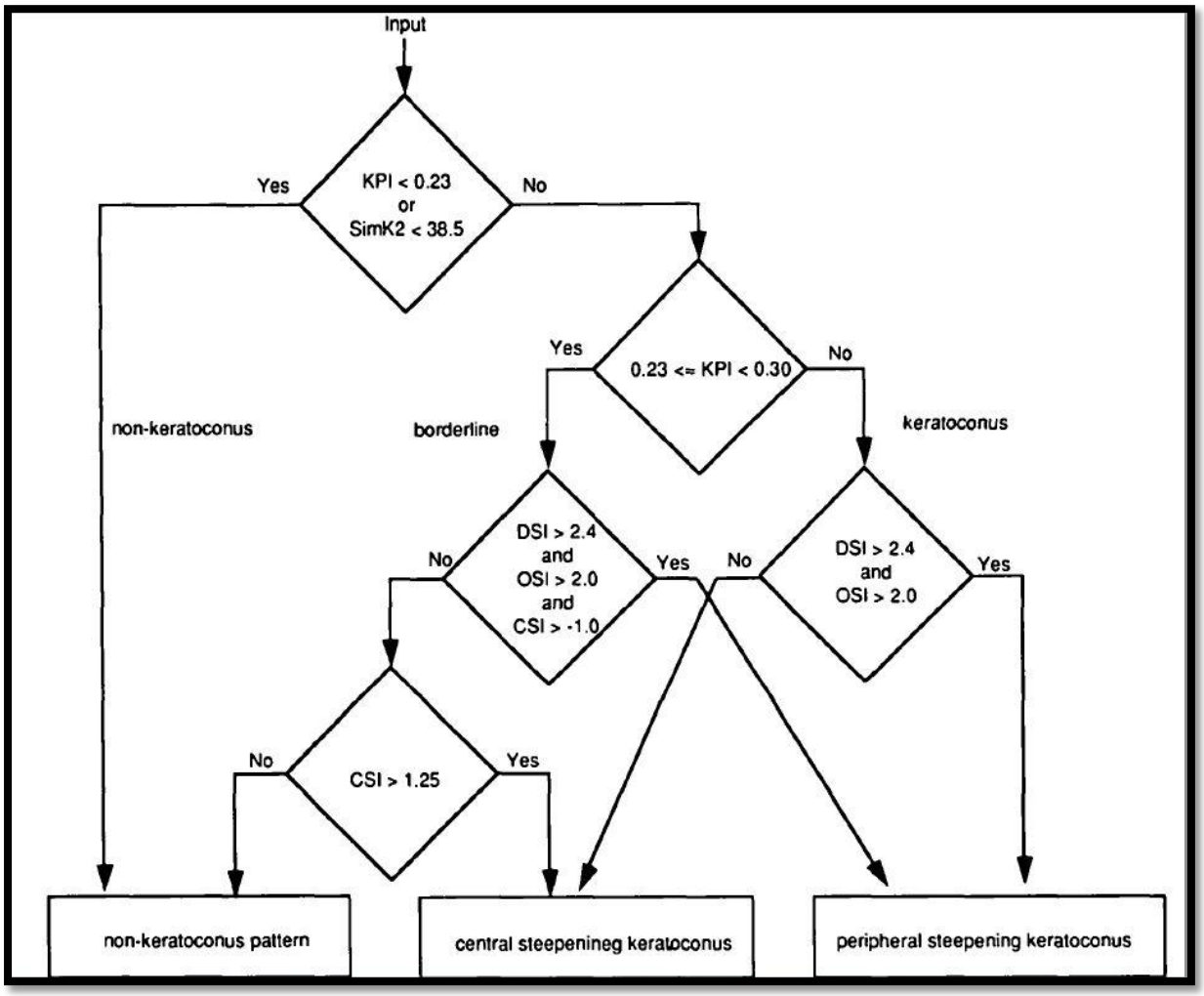
ULTRASOUND PACHYMETER **TOPOGRAPHIC MODELLING SYSTEM IV**

GOLDMANN APPLANATION TONOMETRY

DYNAMIC CONTOUR TONOMETRY

TONOPEN

ANNEXURE VI


Input
KPI < 0.23
or
SimK2 < 38.5
Yes
No
non-keratoconus
0.23 <= KPI < 0.30
Yes
No
borderline
keratoconus
DSI > 2.4
and
OSI > 2.0
and
CSI > -1.0
No
Yes
DSI > 2.4
and
OSI > 2.0
No
Yes
CSI > 1.25
No
Yes
non-keratoconus pattern
central steepenineg keratoconus
peripheral steepening keratoconus